# Glide 4.0

## Quick Start Guide

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# Contents

# Document Conventions

In addition to the use of italics for names of documents, the font conventions that are used in this document are summarized in the table below.

*Table 1.1.*

| Font | Example | Use |
|---|---|---|
| Sans serif | Project Table | Names of GUI features, such as panels, menus, menu items, buttons, and labels |
| Monospace | `$SCHRODINGER/maestro` | File names, directory names, commands, environment variables, and screen output |
| Italic | *filename* | Text that the user must replace with a value |
| Sans serif uppercase | CTRL+H | Keyboard keys |

In descriptions of command syntax, the following UNIX conventions are used: braces `{ }` enclose a choice of required items, square brackets `[ ]` enclose optional items, and the pipe symbol | separates items in a list from which one item must be chosen. Lines of command syntax that wrap should be interpreted as a single command.

In this document, to *type* text means to type the required text in the specified location, and to *enter* text means to type the required text, then press the ENTER key.

References to literature sources are given in square brackets, like this: [10].

# Preparing To Use the Quick Start Guide

## 1.1 About this Document

This manual contains tutorials designed to help you quickly become familiar with the functionality of Glide™, using the Maestro interface. This chapter contains a brief overview of the software and some setup instructions for the tutorials. Chapter 2 contains an introduction to some of the main features of Maestro. The tutorial begins in Chapter 3, with preparation of the protein and ligand complexes. Chapter 4 covers the generation of grids to represent the receptor for docking. In Chapter 5, a set of ligands is docked and scored, and the receptor and ligand poses are examined in Chapter 6.

Panel-specific online help is available for all Glide panels. If you need help with a Glide task, click the Help button, open Maestro's help facility from the Help menu on the main menu bar, or see the *Glide User Manual*. For information about performing tasks from the command line, see the *Glide User Manual* and the *Impact Command Reference Manual*.

## 1.2 About Glide and Maestro

**Glide** is designed to assist you in high-throughput screening of potential ligands based on binding mode and affinity for a given receptor molecule. You can compare ligand scores with those of other test ligands, or compare ligand geometries with those of a reference ligand. Additionally, you can use Glide to generate one or more plausible binding modes for a newly designed ligand. Once you locate favorable structures or bonding conformations with Glide, you can use Liaison™ or QSite™ to obtain binding energies for ligand-receptor pairs.

**Protein Preparation** is usually required for Glide calculations. It can be performed for most protein and protein-ligand complex PDB structures using the Protein Preparation panel in Maestro. Command-line utilities complete the protein preparation facility.

**Maestro** is Schrödinger's powerful, unified, multi-platform graphical user interface (GUI). It is designed to simplify modeling tasks, such as molecule building and data analysis, and also to facilitate the set up and submission of jobs to Schrödinger's computational programs. The main Maestro features include a project-based data management facility, a scripting language for automating large or repetitive tasks, a wide range of useful display options, a comprehensive molecular builder, and surfacing and entry plotting facilities. For more detailed information about the Maestro interface, see Chapter 2 of this manual, the Maestro online help, or the *Maestro User Manual*.

Maestro comes with automatic context-sensitive help (Auto-Help), Balloon Help (tooltips), an online help facility, and a user manual. For more information on getting help, see Section 2.11 on page 30. You can also undo some operations in Maestro. For more information, see Section 2.9 on page 28.

The **Impact** computational engine is the underlying computational program for Glide. It can perform molecular mechanics calculations, either through the Maestro interface or from the command line. For information on running basic Impact jobs, see the Maestro online help or the *Impact Command Reference Manual*.

## 1.3 Preparing a Local Directory Tree

To complete the exercises, you must have access to an installed version of Maestro 7.5 and Glide 4.0. For installation instructions, see the *Installation Guide*.

Exercises in some chapters produce structure files that are needed in subsequent exercises. To allow you to begin at any exercise you choose, these and other necessary files (ligand files, for example) are included with the Glide distribution. The `$SCHRODINGER/impact-v`*version*`/tutorial/` directory and its subdirectories contain the structure files needed in each chapter.

It is useful to create a local directory tree in which you will perform the tutorial exercises: a base directory and subdirectories to work and write files in.

1. In a terminal window, change to a directory in which you have write permission.
2. Create a local tutorial base directory:

   ```
   mkdir tutorial
   ```

   In the text, this directory is referred to as the base directory, or by name as *yourpath*`/tutorial`.
3. In the base directory, create subdirectories named `proteinprep`, `glide`, and `grids`.
4. In the base directory, create a soft link to the `$SCHRODINGER/impact-v`*version*`/tutorial/structures` directory by entering the following command:

   ```
   ln -s $SCHRODINGER/impact-vversion/tutorial/structures .
   ```

## 1.4 Starting Maestro

You do not need to start Maestro until you begin an exercise. If you have not started Maestro before, this section contains instructions.

**To start Maestro:**

1. Set the `SCHRODINGER` environment variable to the directory in which Maestro and Glide are installed:

   **csh/tcsh:** `setenv SCHRODINGER` *installation_path*

   **sh/bash/ksh:** `export SCHRODINGER=`*installation_path*

2. Change to the desired working directory.

   `cd` *working-directory-name*

3. Enter the command:

   `$SCHRODINGER/maestro &`

# Introduction to Maestro

Maestro is the graphical user interface for all of Schrödinger's products: CombiGlide™, Epik™, Glide™, Impact™, Jaguar™, Liaison™, LigPrep™, MacroModel®, Phase™, Prime™, QikProp™, QSite™, SiteMap™, and Strike™. It contains tools for building, displaying, and manipulating chemical structures; for organizing, loading, and storing these structures and associated data; and for setting up, monitoring, and visualizing the results of calculations on these structures. This chapter provides a brief introduction to Maestro and some of its capabilities. For more information on any of the topics in this chapter, see the *Maestro User Manual*.

## 2.1 General Interface Behavior

Most Maestro panels are amodal: more than one panel can be open at a time, and a panel need not be closed for an action to be carried out. Each Maestro panel has a Close button so you can hide the panel from view.

Maestro supports the mouse functions common to many graphical user interfaces. The left button is used for choosing menu items, clicking buttons, and selecting objects by clicking or dragging. This button is also used for resizing and moving panels. The right button displays a shortcut menu. Other common mouse functions are supported, such as using the mouse in combination with the SHIFT or CTRL keys to select a range of items and select or deselect a single item without affecting other items.

In addition, the mouse buttons are used for special functions described later in this chapter. These functions assume that you have a three-button mouse. If you have a two-button mouse, ensure that it is configured for three-button mouse simulation (the middle mouse button is simulated by pressing or holding down both buttons simultaneously).

## 2.2 Starting Maestro

Before starting Maestro, you must first set the `SCHRODINGER` environment variable to point to the installation directory. To set this variable, enter the following command at a shell prompt:

**csh/tcsh:** `setenv SCHRODINGER` *installation-directory*

**bash/ksh:** `export SCHRODINGER=`*installation-directory*

You might also need to set the DISPLAY environment variable, if it is not set automatically when you log in. To determine if you need to set this variable, enter the command:

```
echo $DISPLAY
```

If the response is a blank line, set the variable by entering the following command:

**csh/tcsh:** `setenv DISPLAY` *display-machine-name*`:0.0`

**bash/ksh:** `export DISPLAY=`*display-machine-name*`:0.0`

After you set the SCHRODINGER and DISPLAY environment variables, you can start Maestro using the command:

```
$SCHRODINGER/maestro options
```

If you add the $SCHRODINGER directory to your path, you only need to enter the command maestro. Options for this command are given in Section 2.1 of the *Maestro User Manual*.

The directory from which you started Maestro is Maestro's current working directory, and all data files are written to and read from this directory unless otherwise specified (see Section 2.8 on page 27). You can change directories by entering the following command in the command input area (see page 8) of the main window:

```
cd directory-name
```

where *directory-name* is either a full path or a relative path.

## 2.3 The Maestro Main Window

The Maestro main window is shown in Figure 2.1 on page 7. The main window components are listed below.

The following components are always visible:

- **Title bar**—displays the Maestro version, the project name (if there is one) and the current working directory.
- **Auto-Help**—automatically displays context-sensitive help.
- **Menu bar**—provides access to panels.
- **Workspace**—displays molecular structures and other 3D graphical objects.

The following components can be displayed or hidden by choosing the component from the Display menu. Your choice of which main window components are displayed is persistent between Maestro sessions.

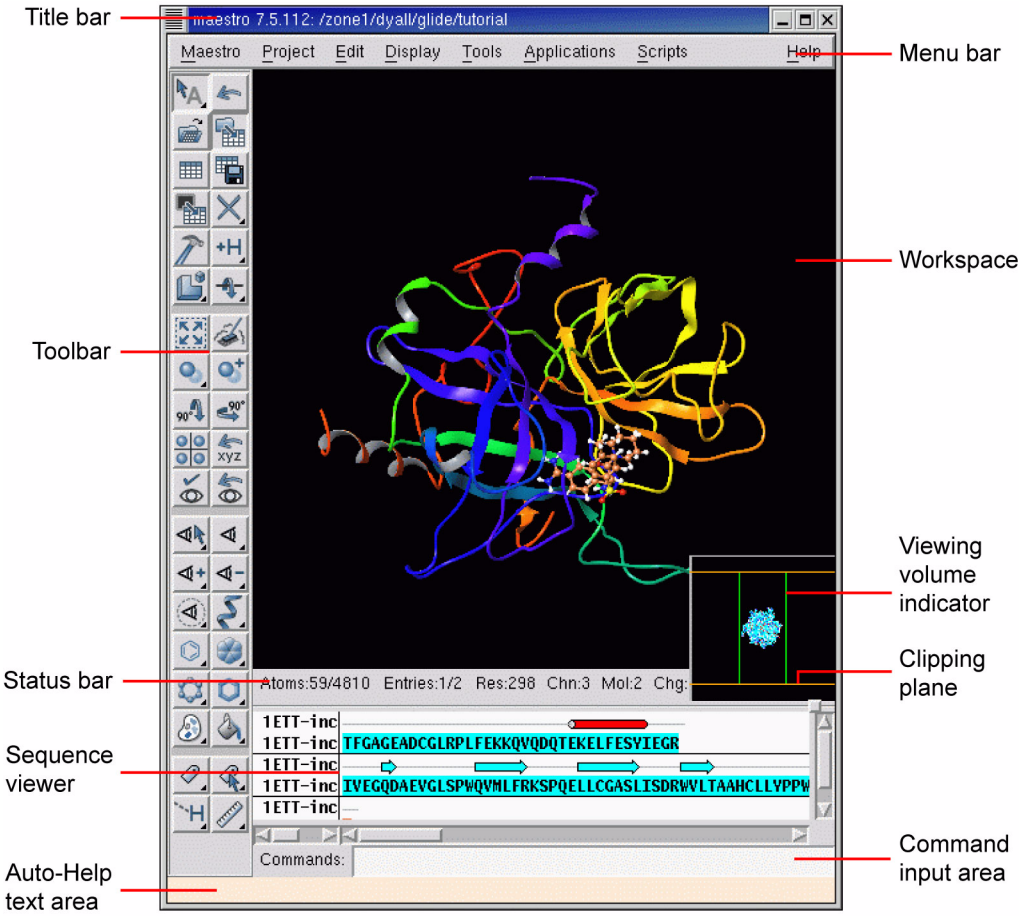


*Figure 2.1. The Maestro main window.*

- **Toolbar**—contains buttons for many common tasks and provides tools for displaying and manipulating structures, as well as organizing the Workspace.
- **Status bar**—displays information about a particular atom, or about structures in the Workspace, depending on where the pointer pauses (see Section 2.5 of the *Maestro User Manual* for details):
  - **Atom**—displays the chain, residue number, element, PDB atom name, formal charge, and title or entry name (this last field is set by choosing Preferences from the Maestro menu and selecting the Feedback folder).
  - **Workspace**—displays the number of atoms, entries, residues, chains, and molecules in the Workspace.

- **Clipping planes window**—displays a small, top view of the Workspace and shows the clipping planes and viewing volume indicators.
- **Sequence viewer**—shows the sequences for proteins displayed in the Workspace. See Section 2.6 of the *Maestro User Manual* for details.
- **Command input area**—provides a place to enter Maestro commands.

When a distinction between components in the main window and those in other panels is needed, the term *main* is applied to the main window components (e.g., main toolbar).

You can expand the Workspace to occupy the full screen, by pressing CTRL+=. All other components and panels are hidden. To return to the previous display, press CTRL+= again.

### 2.3.1 The Menu Bar

The menus on the main menu bar provide access to panels, allow you to execute commands, and control the appearance of the Workspace. The main menus are as follows:

- Maestro—save or print images in the Workspace, execute system commands, save or load a panel layout, set preferences, set up Maestro command aliases, and quit Maestro.
- Project—open and close projects, import and export structures, make a snapshot, and annotate a project. These actions can also be performed from the Project Table panel. For more information, see Section 2.4 on page 13.
- Edit—undo actions, build and modify structures, define command scripts and macros, and find atoms in the Workspace.
- Display—control the display of the contents of the Workspace, arrange panels, and display or hide main window components.
- Tools—group atoms; measure, align, and superimpose structures; and view and visualize data.
- Applications—set up, submit, and monitor jobs for Schrödinger's computational programs. Some products have a submenu from which you can choose the task to be performed.
- Scripts—manage and install Python scripts that come with the distribution and scripts that you create yourself. (See Chapter 13 of the *Maestro User Manual* for details.)
- Help—open the Help panel, the PDF documentation index, or information panels; run a demonstration; and display or hide Balloon Help (tooltips).

## 2.3.2 The Toolbar

The main toolbar contains three kinds of buttons for performing common tasks:

**Action**—Perform a simple task, like clearing the Workspace.

**Display**—Open or close a panel or open a dialog box, such as the Project Table panel.

**Menu**—Display a *button menu*. These buttons have a triangle in the lower right corner.

There are four types of items on button menus, and all four types can be on the same menu (see Figure 2.2):

- **Action**—Perform an action immediately.
- **Display**—Open a panel or dialog box.
- **Object types for selection**—Choose Atoms, Bonds, Residues, Chains, Molecules, or Entries, then click on an atom in the Workspace to perform the action on all the atoms in that structural unit.

  The object type is marked on the menu with a red diamond and the button is indented to indicate the action to be performed.
- **Other setting**—Set a state, choose an attribute, or choose a parameter and click on atoms in the Workspace to display or change that parameter.

The toolbar buttons are described below. Some descriptions refer to features not described in this chapter. See the *Maestro User Manual* for a fuller description of these features.


***Figure 2.2. The*** Workspace selection ***button menu and the*** Adjust distances, angles or dihedrals ***button menu.***

**Workspace selection**
– Choose an object type for selecting
– Open the Atom Selection dialog box

**Undo/Redo**
Undo or redo the last action. Performs the same function as the Undo item on the Edit menu, and changes to an arrow pointing in the opposite direction when an Undo has been performed, indicating that its next action is Redo.

**Open a project**
Open the Open Project dialog box.

**Import structures**
Open the Import panel.

**Open/Close Project Table**
Open the Project Table panel or close it if it is open.

**Save as**
Open the Save Project As dialog box, to save the project with a new name.

**Create entry from Workspace**
Open a dialog box in which you can create an entry in the current project using the contents of the Workspace.

**Delete**
– Choose an object type for deletion
– Delete hydrogens and waters
– Open the Atom Selection dialog box
– Delete other items associated with the structures in the Workspace
– Click to select atoms to delete
– Double-click to delete all atoms

**Open/Close Build panel**
Open the Build panel or close it if it is open.

**Add hydrogens**
– Choose an object type for applying a hydrogen treatment
– Open the Atom Selection dialog box
– Click to select atoms to treat
– Double-click to apply to all atoms

**Local transformation**
– Choose an object type for transforming
– Click to select atoms to transform
– Open the Advanced Transformations panel

**Adjust distances, angles or dihedrals**
– Choose a parameter for adjusting
– Delete adjustments

**Fit to screen**
Scale the displayed structure to fit into the Workspace and reset the center of rotation.

**Clear Workspace**
Clear all atoms from the Workspace.

**Set fog display state**
Choose a fog state. Automatic means fog is on when there are more than 40 atoms in the Workspace, otherwise it is off.

**Enhance depth cues**
Optimize fogging and other depth cues based on what is in the Workspace.

**Rotate around X axis by 90 degrees**
Rotate the Workspace contents around the X axis by 90 degrees.


**Rotate around Y axis by 90 degrees**
Rotate the Workspace contents around the Y axis by 90 degrees.

Tile entries
Arrange entries in a rectangular grid in the Workspace.


Reset Workspace
Reset the rotation, translation, and zoom of the Workspace to the default state.

Save view
Save the current view of the Workspace: orientation, location, and zoom.

Restore view
Restore the last saved view of the Workspace: orientation, location, and zoom.

Display only selected atoms
– Choose an object type for displaying
– Click to select atoms to display
– Double-click to display all atoms

Display only
– Choose a predefined atom category
– Open the Atom Selection dialog box

Also display
– Choose a predefined atom category
– Open the Atom Selection dialog box

Undisplay
– Choose a predefined atom category
– Open the Atom Selection dialog box

Display residues within N angstroms of currently displayed atoms
– Choose a radius
– Open a dialog box to set a value

Show, hide, or color ribbons
– Choose to show or hide ribbons
– Choose a color scheme for coloring ribbons

Draw bonds in wire
– Choose an object type for drawing bonds in wire representation
– Open the Atom Selection dialog box
– Click to select atoms for representation
– Double-click to apply to all atoms

Draw atoms in CPK
– Choose an object type for drawing bonds in CPK representation
– Open the Atom Selection dialog box
– Click to select atoms for representation
– Double-click to apply to all atoms

Draw atoms in Ball & Stick
– Choose an object type for drawing bonds in Ball & Stick representation
– Open the Atom Selection dialog box
– Click to select atoms for representation
– Double-click to apply to all atoms

Draw bonds in tube
– Choose an object type for drawing bonds in tube representation
– Open the Atom Selection dialog box
– Click to select atoms for representation
– Double-click to apply to all atoms

Color all atoms by scheme
Choose a predefined color scheme.

Color residue by constant color
– Choose a color for applying to residues
– Click to select residues to color
– Double-click to color all atoms

Label atoms
– Choose a predefined label type
– Delete labels

Label picked atoms
– Choose an object type for labeling atoms
– Open the Atom Selection dialog box
– Open the Atom Labels panel at the Composition folder
– Delete labels
– Click to select atoms to label
– Double-click to label all atoms

Display H-bonds
– Choose bond type:
intra—displays H-bonds within the selected molecule
inter—displays H-bonds between the selected molecule and all other atoms.
– Delete H-bonds
– Click to select molecule

Measure distances, angles or dihedrals
– Choose a parameter for displaying measurements
– Delete measurements
– Click to select atoms for measurement

### 2.3.3 Mouse Functions in the Workspace

The left mouse button is used for selecting objects. You can either click on a single atom or bond, or you can drag to select multiple objects. The right mouse button opens shortcut menus, which are described in Section 2.7 of the *Maestro User Manual*.

The middle and right mouse buttons can be used on their own and in combination with the SHIFT and CTRL keys to perform common operations, such as rotating, translating, centering, adjusting, and zooming.

*Table 2.1. Mapping of Workspace operations to mouse actions.*

| Mouse Button | Keyboard | Motion | Action |
|---|---|---|---|
| Left | | click, drag | Select |
| Left | SHIFT | click, drag | Toggle the selection |
| Middle | | drag | Rotate about X and Y axes<br>Adjust bond, angle, or dihedral |
| Middle | SHIFT | drag vertically | Rotate about X axis |
| Middle | SHIFT | drag horizontally | Rotate about Y axis |
| Middle | CTRL | drag horizontally | Rotate about Z axis |
| Middle | SHIFT + CTRL | drag horizontally | Zoom |
| Right | | click | Spot-center on selection |
| Right | | click and hold | Display shortcut menu |
| Right | | drag | Translate in the X-Y plane |
| Right | SHIFT | drag vertically | Translate along the X axis |
| Right | SHIFT | drag horizontally | Translate along the Y axis |
| Right | CTRL | drag horizontally | Translate along the Z axis |
| Middle & Right | | drag horizontally | Zoom |

### 2.3.4 Shortcut Key Combinations

Some frequently used operations have been assigned shortcut key combinations. The shortcuts available in the main window are described in Table 2.2.

*Table 2.2. Shortcut keys in the Maestro main window.*

| Keys | Action | Equivalent Menu Choices |
|---|---|---|
| CTRL+B | Open Build panel | Edit > Build |
| CTRL+C | Create entry | Project > Create Entry From Workspace |
| CTRL+E | Open Command Script Editor panel | Edit > Command Script Editor |
| CTRL+F | Open Find Atoms panel | Edit > Find |
| CTRL+H | Open Help panel | Help > Help |
| CTRL+I | Open Import panel | Project > Import Structures |
| CTRL+M | Open Measurements panel | Tools > Measurements |
| CTRL+N | Create new project | Project > New |
| CTRL+O | Open project | Project > Open |
| CTRL+P | Print | Maestro > Print |
| CTRL+Q | Quit | Maestro > Quit |
| CTRL+S | Open Sets panel | Tools > Sets |
| CTRL+T | Open Project Table panel | Project > Show Table |
| CTRL+W | Close project | Project > Close |
| CTRL+Z | Undo/Redo last command | Edit > Undo/Redo |
| CTRL+= | Enter and exit full screen mode (Workspace occupies full screen) | None |

## 2.4 Maestro Projects

All the work you do in Maestro is done within a *project*. A project consists of a set of *entries*, each of which contains one or more chemical structures and their associated data. In any Maestro session, there can be only one Maestro project open. If you do not specify a project when you start Maestro, a *scratch* project is created. You can work in a scratch project without saving it, but you must save it in order to use it in future sessions. When you save or close a project, all the view transformations (rotation, translation, and zoom) are saved with it. When you close a project, a new scratch project is automatically created.

Likewise, if there is no entry displayed in the Workspace, Maestro creates a *scratch* entry. Structures that you build in the Workspace constitute a scratch entry until you save the structures as project entries. The scratch entry is not saved with the project unless you explicitly add it to the project. However, you can use a scratch entry as input for some calculations.

To add a scratch entry to a project, do one of the following:

- Click the Create entry from Workspace button:

- Choose Create Entry from Workspace from the Project menu.
- Press CTRL+C.

In the dialog box, enter a name and a title for the entry. The entry name is used internally to identify the entry and can be modified by Maestro. The title can be set or changed by the user, but is not otherwise modified by Maestro.

Once an entry has been incorporated into the project, its structures and their data are represented by a row in the Project Table. Each row contains the row number, an icon indicating whether the entry is displayed in the Workspace (the In column), the entry title, a button to open the Surfaces panel if the entry has surfaces, the entry name, and any entry properties. The row number is not a property of the entry.

Entries can be collected into groups, and the members of the group can be displayed or hidden. Most additions of multiple entries to the Project Table are done as entry groups.

You can use entries as input for all of the computational programs—Glide, Impact, Jaguar, Liaison, LigPrep, MacroModel, Phase, Prime, QikProp, QSite, and Strike. You can select entries as input for the ePlayer, which displays the selected structures in sequence. You can also duplicate, combine, rename, and sort entries; create properties; import structures as entries; and export structures and properties from entries in various formats.

To open the Project Table panel, do one of the following:

- Click the Open/Close Project Table button on the toolbar

- Choose Show Table from the Project menu
- Press CTRL+T.

The Project Table panel contains a menu bar, a toolbar, and the table itself.

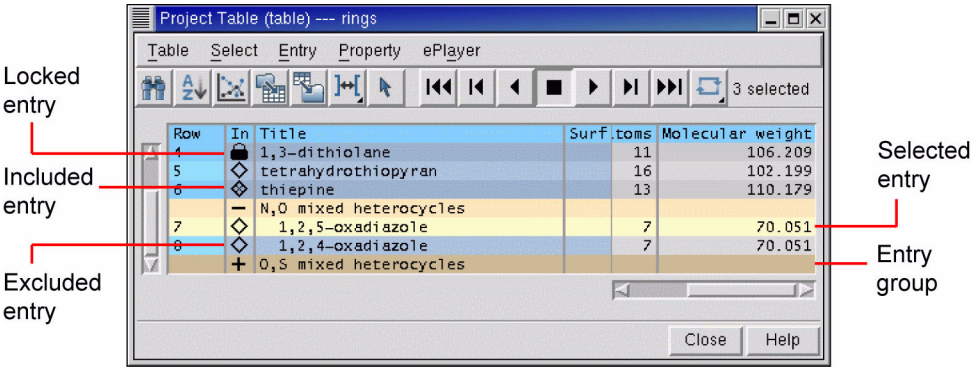


***Figure 2.3. The** Project Table **panel.***

## 2.4.1 The Project Table Toolbar

The Project Table toolbar contains two groups of buttons and a status display. The first set of buttons opens various panels that allow you to perform functions on the entries in the Project Table. The second set of buttons controls the ePlayer, which "plays through" the selected structures: each structure is displayed in the Workspace in sequence, at a given time interval. See Section 2.3.2 on page 9 for a description of the types of toolbar buttons. The buttons are described below.

Find
Open the Find panel for locating alphanumeric text in any column of the Project Table, except for the row number.

Sort
Open the Sort panel for sorting entries by up to three properties.

Plot
Open the Plot panel for plotting entry properties.

Import Structure
Open the Import panel for importing structures into the project.

Export Structure
Open the Export panel for exporting structures to a file.

Columns
Choose an option for adjusting the column widths.

Select only
Open the Entry Selection dialog box for selecting entries based on criteria for entry properties.

Go to start
Display the first selected structure.

Previous
Display the previous structure in the list of selected structures.

Play backward
Display the selected structures in sequence, moving toward the first.

Stop
Stop the ePlayer.

Play forward
Display the selected structures in sequence, moving toward the last.

Next
Display the next structure in the list of selected structures.

Go to end
Display the last selected structure.

Loop
Choose an option for repeating the display of the structures. Single Direction displays structures in a single direction, then repeats. Oscillate reverses direction each time the beginning or end of the list is reached.

The status display, to the right of the toolbar buttons, shows the number of selected entries. When you pause the cursor over the status display, the Balloon Help shows the total number of entries, the number shown in the table, the number selected, and the number included in the Workspace.

### 2.4.2 The Project Table Menus

- Table—find text, sort entries, plot properties, import and export structures, and configure the Project Table.
- Select—select all entries, none, invert your selection, or select classes of entries using the Entry Selection dialog box and the Filter panel.
- Entry—include or exclude entries from the Workspace, display or hide entries in the Project Table, and perform various operations on the selected entries.
- Property—display and manipulate entry properties in the Project Table.
- ePlayer—view entries in succession, stop, reverse, and set the ePlayer options.

### 2.4.3 Selecting Entries

Many operations in Maestro are performed on the entries selected in the Project Table. The Project Table functions much like any other table: select rows by clicking, shift-clicking, and control-clicking. However, because clicking in an editable cell of a selected row enters edit mode, you should click in the Row column to select entries. See Section 2.4.5 on page 18 for more information on mouse actions in the Project Table. There are shortcuts for selecting classes of entries on the Select menu.

In addition to selecting entries manually, you can select entries that meet a combination of conditions on their properties. Such combinations of conditions are called *filters*. Filters are Entry Selection Language (ESL) expressions and are evaluated at the time they are applied. For example, if you want to set up a Glide job that uses ligands with a low molecular weight (say, less than 300) and that has certain QikProp properties, you can set up a filter and use it to select entries for the job. If you save the filter, you can use it again on a different set of ligands that meet the same selection criteria.

**To create a filter:**

1. Do one of the following:
   - Choose Only, Add, or Deselect from the Select menu.
   - Click the Entry selection button on the toolbar.

   
2. In the Properties folder, select a property from the property list, then select a condition.
3. Combine this selection with the current filter by clicking Add, Subtract, or Intersect. These buttons perform the Boolean operations OR, AND NOT, and AND on the corresponding ESL expressions.
4. To save the filter for future use click Create Filter, enter a name, and click OK.
5. Click OK to apply the filter immediately.

### 2.4.4 Including Entries in the Workspace

In addition to selecting entries, you can also use the Project Table to control which entries are displayed in the Workspace. An entry that is displayed in the Workspace is *included* in the Workspace; likewise, an entry that is not displayed is *excluded*. Included entries are marked by an X in the diamond in the In column; excluded entries are marked by an empty diamond. Entry inclusion is completely independent of entry selection.

To include or exclude entries, click, shift-click, or control-click in the In column of the entries, or select entries and choose Include or Exclude from the Entry menu. Inclusion with the mouse works just like selection: when you include an entry by clicking, all other entries are excluded.

It is sometimes useful to keep one entry in the Workspace and include others one by one: for example, a receptor and a set of ligands. You can fix the receptor in the Workspace by selecting it in the Project Table and choosing Fix from the Entry menu or by pressing CTRL+F. A padlock icon replaces the diamond in the In column to denote a *fixed* entry. To remove a fixed entry from the Workspace, you must exclude it explicitly (CTRL+X). It is not affected by the inclusion or exclusion of other entries. Fixing an entry affects only its inclusion; you can still rotate, translate, or modify the structure.

### 2.4.5 Mouse Functions in the Project Table

The Project Table supports the standard use of shift-click and control-click to select objects. This behavior applies to the selection of entries and the inclusion of entries in the Workspace. You can also drag to resize rows and columns and to move rows.

You can drag a set of non-contiguous entries to reposition them in the Project Table. When you release the mouse button, the entries are placed after the first unselected entry that precedes the entry on which the cursor is resting. For example, if you select entries 2, 4, and 6, and release the mouse button on entry 3, these three entries are placed after entry 1, because entry 1 is the first unselected entry that precedes entry 3. To move entries to the top of the table, drag them above the top of the table; to move entries to the end of the table, drag them below the end of the table.

A summary of mouse functions in the Project Table is provided in Table 2.3.

*Table 2.3. Mouse operations in the Project Table.*

| Task | Mouse Operation |
|---|---|
| Change a Boolean property value | Click repeatedly in a cell to cycle through the possible values (On, Off, Clear) |
| Display the Entry menu for an entry | Right-click anywhere in the entry. If the entry is not selected, it becomes the selected entry. If the entry is selected, the action is applied to all selected entries. |
| Display a version of the Property menu for a property | Right-click in the column header |
| Edit the text or the value in a table cell | Click in the cell and edit the text or value |
| Include an entry in the Workspace, exclude all others | Click the In column of the entry |

*Table 2.3. Mouse operations in the Project Table. (Continued)*

| Task | Mouse Operation |
|---|---|
| Move selected entries | Drag the entries |
| Paste text into a table cell | Middle-click |
| Resize rows or columns | Drag the boundary with the middle mouse button |
| Select an entry, deselect all others | For an unselected entry, click anywhere in the row except the In column; for a selected entry, click the row number. |
| Select or include multiple entries | Click the first entry then shift-click the last entry |
| Toggle the selection or inclusion state | Control-click the entry or the In column |

## 2.4.6 Project Table Shortcut Keys

Some frequently used project operations have been assigned shortcut key combinations. The shortcuts, their functions, and their menu equivalents are listed in Table 2.4.

*Table 2.4. Shortcut keys in the Project Table.*

| Keys | Action | Equivalent Menu Choices |
|---|---|---|
| CTRL+A | Select all entries | Select > All |
| CTRL+F | Fix entry in Workspace | Entry > Fix |
| CTRL+I | Open Import panel | Table > Import Structures |
| CTRL+N | Include only selected entries | Entry > Include Only |
| CTRL+U | Deselect all entries | Select > None |
| CTRL+X | Exclude selected entries | Entry > Exclude |
| CTRL+Z | Undo/Redo last command | Edit > Undo/Redo in main window |

## 2.5 Building a Structure

After you start Maestro, the first task is usually to create or import a structure. You can open existing Maestro projects or import structures from other sources to obtain a structure, or you can build your own. To open the Build panel, do one of the following:

- Click the Open/Close Build panel button in the toolbar:

- Choose Build from the Edit menu.
- Press CTRL+B.

The Build panel allows you to create structures by drawing or placing atoms or fragments in the Workspace and connecting them into a larger structure, to adjust atom positions and bond orders, and to change atom properties. This panel contains a toolbar and three folders.

### 2.5.1 Placing and Connecting Fragments

The Build panel provides several tools for creating structures in the Workspace. You can place and connect fragments, or you can draw a structure freehand.

**To place a fragment in the Workspace:**

1. Select Place.
2. Choose a fragment library from the Fragments menu.
3. Click a fragment.
4. Click in the Workspace where you want the fragment to be placed.

**To connect fragments in the Workspace, do one of the following:**

- Place another fragment and connect them using the Connect & Fuse panel, which you open from the Edit menu on the main menu bar or with the Display Connect & Fuse panel on the Build toolbar.

- Replace one or more atoms in the existing fragment with another fragment by selecting a fragment and clicking in the Workspace on the main atom to be replaced.
- Grow another fragment by selecting Grow in the Build panel and clicking the fragment you want to add in the Fragments folder.

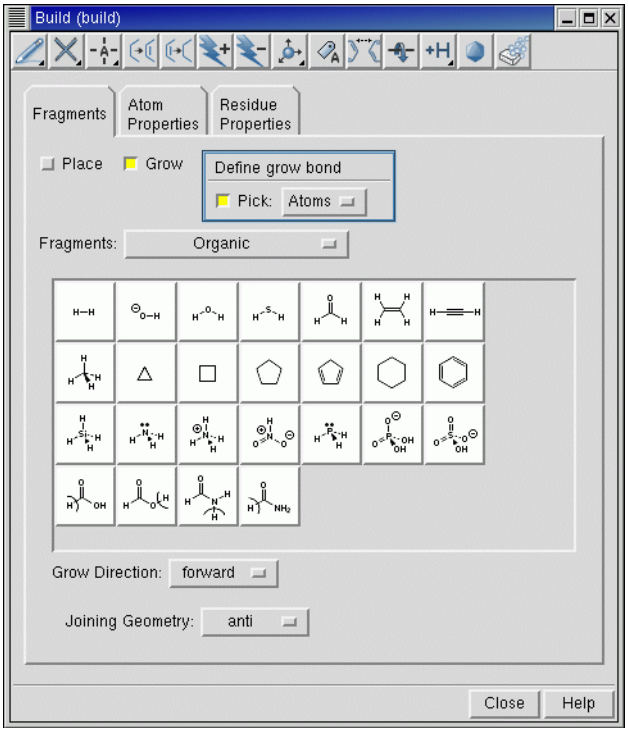


***Figure 2.4. The* Build *panel.***

Grow mode uses predefined rules to connect a fragment to the *grow bond*. The grow bond is marked by a green arrow. The new fragment replaces the atom at the head of the arrow on the grow bond and all atoms attached to it. To change the grow bond, choose Bonds from the Pick option menu in the Build panel and click on the desired grow bond in the Workspace. The arrow points to the atom nearest to where you clicked.

**To draw a structure freehand:**

1. Choose an element from the Draw button menu on the Build panel toolbar:

   

2. Click in the Workspace to place an atom of that element.
3. Click again to place another atom and connect it to the previous atom.
4. Continue this process until you have drawn the structure.
5. Click the active atom again to finish drawing.

### 2.5.2 Adjusting Properties

In the Atom Properties folder, you can change the properties of the atoms in the Workspace. For each item on the Property option menu—Element, Atom Type (MacroModel), Partial Charge, PDB Atom Name, Grow Name, and Atom Name—there is a set of tools you can use to change the atom properties. For example, the Element tools consist of a periodic table from which you can choose an element and select an atom to change it to an atom of the selected element.

Similarly, the Residue Properties folder provides tools for changing the properties of residues: the Residue Number, the Residue Name, and the Chain Name.

To adjust bond lengths, bond angles, dihedral angles, and chiralities during or after building a structure, use the Adjust distances, angles or dihedrals button on the main toolbar:

You can also open the Adjust panel from this button menu, from the Display Adjust panel button on the Build panel toolbar (which has the same appearance as the above button) or from the Edit menu in the main window.

### 2.5.3 The Build Panel Toolbar

The toolbar of the Build panel provides quick access to tools for drawing and modifying structures and labeling atoms. See Section 2.3.2 on page 9 for a description of the types of toolbar buttons. The toolbar buttons and their use are described below.

Free-hand drawing
Choose an element for drawing structures freehand in the Workspace (default C). Each click in the Workspace places an atom and connects it to the previous atom.

Delete
Choose an object for deleting. Same as the Delete button on the main toolbar, see page 10.

Set element
Choose an element for changing atoms in the Workspace (default C). Click an atom to change it to the selected element.

Increment bond order
Select a bond to increase its bond order by one, to a maximum of 3.

Decrement bond order
Select a bond to decrease its bond order by one, to a minimum of 0.

Increment formal charge
Select an atom to increase its formal charge by one.

Decrement formal charge
Select an atom to decrease its formal charge by one.

Move
Choose a direction for moving atoms, then click the atom to be moved. Moves in the XY plane are made by clicking the new location. Moves in the Z direction are made in 0.5 Å increments.

Label
Apply heteroatom labels as you build a structure. The label consists of the element name and formal charge, and is applied to atoms other than C and H.

Display Connect & Fuse panel
Open the Connect & Fuse panel so you can connect structures (create bonds between structures) or fuse structures (replace atoms of one structure with those of another).

Display Adjust panel
Open the Adjust panel so you can change bond lengths, bond angles, dihedral angles, or atom chiralities.

Add hydrogens
Choose an atom type for applying the current hydrogen treatment. Same as the Add hydrogens button on the main toolbar, see page 10.

Geometry Symmetrizer
Open the Geometry Symmetrizer panel for symmetrizing the geometry of the structure in the Workspace.

Geometry Cleanup
Clean up the geometry of the structure in the Workspace.

## 2.6 Selecting Atoms

Maestro has a powerful set of tools for selecting atoms in a structure: toolbar buttons, picking tools in panels, and the Atom Selection dialog box. These tools allow you to select atoms in two ways:

- Select atoms first and apply an action to them
- Choose an action first and then select atoms for that action

### 2.6.1 Toolbar Buttons

The small triangle in the lower right corner of a toolbar button indicates that the button contains a menu. Many of these buttons allow you to choose an object type for selecting: choose Atoms, Bonds, Residues, Chains, Molecules, or Entries, then click on an atom in the Workspace to perform the action on all the atoms in that structural unit.

For example, to select atoms with the Workspace selection toolbar button:

1. Choose Residues from the Workspace selection button menu:

   

   The button changes to:

   

2. Click on an atom in a residue in the Workspace to select all the atoms in that residue.

### 2.6.2 Picking Tools

The picking tools are embedded in each panel in which you need to select atoms to apply an operation. The picking tools in a panel can include one or more of the following:

- Pick option menu—Allows you to choose an object type. Depending on the operation to be performed, you can choose Atoms, Bonds, Residues, Chains, Molecules, or Entries, then click on an atom in the Workspace to perform the action on all the atoms in that structural unit.

  The Pick option menu varies from panel to panel, because not all object types are appropriate for a given operation. For example, some panels have only Atoms and Bonds in the Pick option menu.

- All button—Performs the action on all atoms in the Workspace.
- Selection button—Performs the action on any atoms already selected in the Workspace.
- Previous button—Performs the action on the most recent atom selection defined in the Atom Selection dialog box.
- Select button—Opens the Atom Selection dialog box.
- ASL text box—Allows you to type in an ASL expression for selecting atoms.

  ASL stands for Atom Specification Language, and is described in detail in the *Maestro Command Reference Manual*.

- Clear button—Clears the current selection

  

- Show markers option—Marks the selected atoms in the Workspace.

For example, to label atoms with the Label Atoms panel:

1. Choose Atom Labels from the Display menu.
2. In the Composition folder, select Element and Atom Number.
3. In the picking tools section at the top of the panel, you could do one of the following:
   - Click Selection to apply labels to the atoms already selected in the Workspace (from the previous example).
   - Choose Residues from the Pick option menu and click on an atom in a different residue to label all the atoms in that residue.

### 2.6.3 The Atom Selection Dialog Box

If you wish to select atoms based on more complex criteria, you can use the Atom Selection dialog box. To open this dialog box, choose Select from a button menu or click the Select button in a panel. See Section 5.3 of the *Maestro User Manual* for detailed instructions on how to use the Atom Selection dialog box.

## 2.7 Scripting in Maestro

Although you can perform nearly all Maestro-supported operations through menus and panels, you can also perform operations using Maestro commands, or compilations of these commands, called *scripts*. Scripts can be used to automate lengthy procedures or repetitive tasks and can be created in several ways. These are summarized below.

### 2.7.1 Python Scripts

Python is a full-featured scripting language that has been embedded in Maestro to extend its scripting facilities. The Python capabilities within Maestro include access to Maestro functionality for dealing with chemical structures, projects, and Maestro files.

The two main Python commands used in Maestro are:

- `pythonrun`—executes a Python module. (You can also use the alias `pyrun`.) The syntax is:

  `pythonrun` *module*`.`*function*

- `pythonimport`—rereads a Python file so that the next time you use the `pythonrun` command, it uses the updated version of the module. (You can also use the alias `pyimp`.)

From the Maestro Scripts menu you can install, manage, and run Python scripts. For more information on the Scripts menu, see Section 13.1 of the *Maestro User Manual*.

For more information on using Python with Maestro, see *Scripting with Python*.

### 2.7.2 Command Scripts

All Maestro commands are logged and displayed in the Command Script Editor panel. This means you can create a command script by performing the operations with the GUI controls, copying the logged commands from the Command History list into the Script text area of the panel, then saving the list of copied commands as a script.

**To run an existing command script:**

1. Open the Command Script Editor panel from the Edit menu in the main window.
2. Click Open Local and navigate to the directory containing the desired script.
3. Select a script in the Files list and click Open.

   The script is loaded into the Script window of the Command Script Editor panel.
4. Click Run Script.

Command scripts cannot be used for Prime operations.

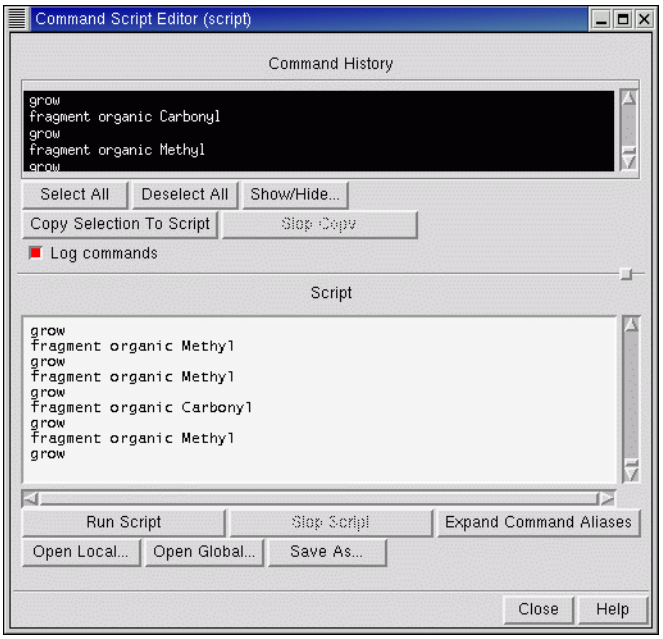


***Figure 2.5. The*** Command Script Editor ***panel.***

### 2.7.3 Macros

There are two kinds of macros you can create: named macros and macros assigned to function keys F1 through F12.

**To create and run a named macro:**

1. Open the Macros panel from the Edit menu in the main window.
2. Click New, enter a name for the macro, and click OK.
3. In the Definition text box, type the commands for the macro.
4. Click Update to update the macro definition.
5. To run the macro, enter the following in the command input area in the main window:

   `macrorun` *macro-name*

   If the command input area is not visible, choose Command Input Area from the Display menu.

**To create and run a function key macro:**

1. Open the Function Key Macros panel from the Edit menu in the main window.
2. From the Macro Key option, select a function key (F1 through F12) to which to assign the macro.
3. In the text box, type the commands for the macro.
4. Click Run to test the macro or click Save to save it.
5. To run the macro from the main window, press the assigned function key.

For more information on macros, see Section 13.5 of the *Maestro User Manual*.

## 2.8 Specifying a Maestro Working Directory

When you use Maestro to launch Glide jobs, Maestro writes job output to the directory specified in the Directory folder of the Preferences panel. By default, this directory (the file I/O directory) is the directory from which you started Maestro.

**To change the Maestro working directory:**

1. Open the Preferences panel from the Maestro menu.
2. Click the Directory tab.
3. Select the directory you want to use for reading and writing files.

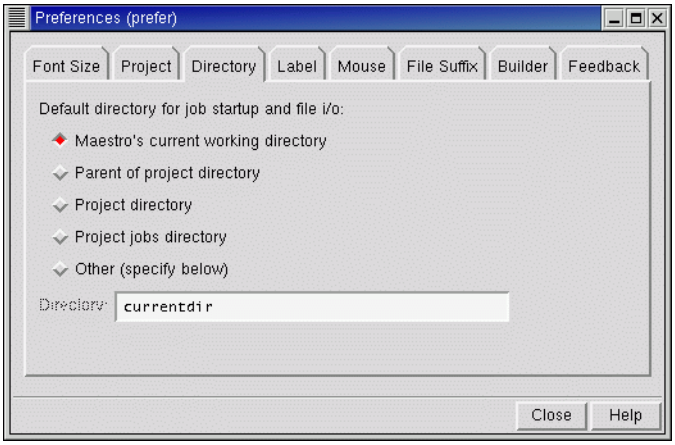


***Figure 2.6. The** Directory **folder of the** Preferences **panel.***

You can also set other preferences in the Preferences panel. See Section 12.2 of the *Maestro User Manual* for details.

## 2.9 Undoing an Operation

To undo a single operation, click the Undo button in the toolbar, choose Undo from the Edit menu, or press CTRL+Z. The word Undo in the menu is followed by text that describes the operation to undo. Not all operations can be undone: for example, global rotations and translations are not undoable operations. For such operations you can use the Save view and Restore view buttons in the toolbar, which save and restore a molecular orientation.

## 2.10 Running and Monitoring Jobs

Maestro has panels for each product for preparing and submitting jobs. To use these panels, choose the appropriate product and task from the Applications menu and its submenus. Set the appropriate options in the panel, then click Start to open the Start dialog box and set options for running the job. For a complete description of the Start dialog box associated with your computational program, see your product's User Manual. When you have finished setting the options, click Start to launch the job and open the Monitor panel.

The Monitor panel is the control panel for monitoring the progress of jobs and for pausing, resuming, or killing jobs. All jobs that belong to you can be displayed in the Monitor panel, whether or not they were started from Maestro. Subjobs are indented under their parent in the job list. The text pane shows output information from the monitored job, such as the contents

of the log file. The Monitor panel opens automatically when you start a job. If it is not open, you can open it by choosing Monitor from the Applications menu in the Maestro main window.

While jobs are running, the Detach, Pause, Resume, Stop, Kill, and Update buttons are active. When there are no jobs currently running, only the Monitor and Delete buttons are active. These buttons act on the selected job. By default, only jobs started from the current project are shown. To show other jobs, deselect Show jobs from current project only.

When a monitored job ends, the results are incorporated into the project according to the settings used to launch the job. If a job that is not currently being monitored ends, you can select it in the Monitor panel and click Monitor to incorporate the results. Monitored jobs are incorporated only if they are part of the current project. You can monitor jobs that are not part of the current project, but their results are not incorporated. To add their results to a project, you must open the project and import the results.

Further information on job control, including configuring your site, monitoring jobs, running jobs, and job incorporation, can be found in the *Job Control Guide* and the *Installation Guide*.

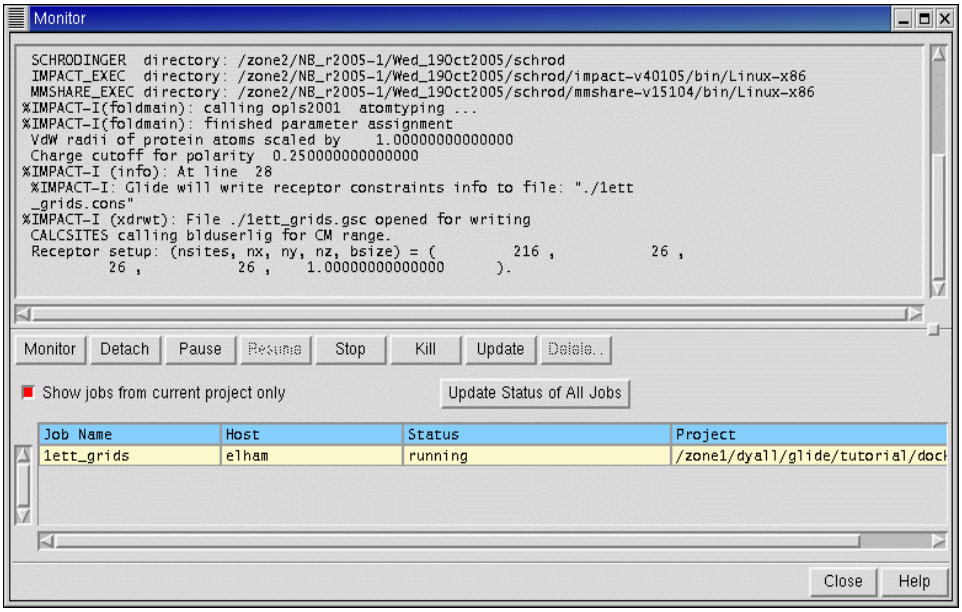


***Figure 2.7. The* Monitor *panel.***

## 2.11 Getting Help

Maestro comes with automatic, context-sensitive help (Auto-Help), Balloon Help (tooltips), an online help facility, and a user manual. To get help, follow the steps below:

- Check the Auto-Help text box at the bottom of the main window. If help is available for the task you are performing, it is automatically displayed there. It describes what actions are needed to perform the task.
- If your question concerns a GUI element, such as a button or option, there may be Balloon Help for the item. Pause the cursor over the element. If the Balloon Help does not appear, check that Show Balloon Help is selected in the Help menu of the main window. If there is Balloon Help for the element, it appears within a few seconds.
- If you do not find the help you need using either of the steps above, click the Help button in the lower right corner of the appropriate panel. The Help panel is displayed with a relevant help topic.
- For help with a concept or action not associated with a panel, open the Help panel from the Help menu or press CTRL+H.

If you do not find the information you need in the Maestro help system, check the following sources:

- The *Maestro User Manual*
- The Frequently Asked Questions page on the Schrödinger Support Center.

You can also contact Schrödinger by e-mail or phone for help:

- E-mail: help@schrodinger.com
- Phone: (503) 299-1150

## 2.12 Ending a Maestro Session

To end a Maestro session, choose Quit from the Maestro menu. To save a log file with a record of all operations performed in the current session, click Quit, save log file in the Quit panel. This information can be useful to Schrödinger support staff when responding to any problem you report.

# Protein and Ligand Preparation

## 3.1 Preparing Proteins for Glide

The quality of the results obtained from Glide depends critically on the quality of the starting structures. These starting structures must include all hydrogens, have correct charge states near the binding site, and be reasonably free of major steric clashes. A typical PDB protein complex structure, as downloaded from the Research Collaboratory for Structural Bioinformatics (RCSB) web site (http://www.rcsb.org[1]), has no hydrogens and may have residues in unusual charge states. Schrödinger offers a Protein Preparation facility for use with Glide that is designed to ensure chemical correctness and to optimize protein structures.

The full Protein Preparation facility includes the Protein Preparation panel, the `protprep` command-line application, and other utilities. See Chapter 4 of the *Glide User Manual* for a description of all the steps and options available. For most structures, however, including the one used in this tutorial, Protein Preparation can be performed in a few steps with Maestro and the Protein Preparation panel.

This tutorial carries out protein preparation for the complex 1ETT: bovine thrombin with cocrystallized ligand 4-TAPAP. Ligand bond orders and formal charges are corrected using the Maestro Build panel. The remaining preparation and refinement tasks run automatically as a job that is set up and started from the Protein Preparation panel.

The 1ETT structure is not a multimer and does not include cofactors or metal ions. See Section 4.5 and Section 4.6 of the *Glide User Manual* for information on preparing systems with these features.

Because this exercise starts by downloading the 1ETT structure from the Protein Data Bank, it does not require any structure files from the `tutorial/structures` directory. The output of this exercise, a fully prepared structure for the 1ETT complex, is used in Chapter 4. However, the `tutorial/structures` directory contains a copy of this complex in PDB format for your convenience.

1. Please see the notice regarding third party programs and third party Web sites on the copyright page at the front of this manual.

## 3.2 Starting Maestro

If you have not yet created a local directory tree, do so now, using the instructions in Section 1.3. Once you have done so, begin the Protein Preparation tutorial:

1. Change to your `proteinprep` directory.
2. Start Maestro. (If you have not started Maestro before, see Section 1.4.)

## 3.3 Importing the Protein Complex Structure

**Download the 1ett complex structure from the Protein Data Bank:**

1. In your browser, go to http://www.rcsb.org/pdb[2].
2. Search the Archive by PDB ID for `1ETT`.
3. Click Download/Display File and download the appropriate PDB file.
4. Uncompress the file if necessary.

**Import `1ETT.pdb` into Maestro:**

1. On the Maestro toolbar, click the Import structures button.

   

   The Import panel is displayed.
2. From the Format options, select PDB.
3. Navigate to the directory in which you saved `1ETT.pdb`.
4. Select `1ETT.pdb` in the Files list and click Import.

   A warning dialog box appears. The problem found while converting this structure is the ligand, which is not a standard residue, but does not need correction.
5. Click OK.

   The protein complex appears in the Workspace. In the project table, it has been added as an entry named 1ETT.

2. Please see the notice regarding third party programs and third party Web sites on the copyright page at the front of this manual.

When Maestro imports a PDB file, standard residues in the imported structure are shown in light gray, while problematic areas, such as structural errors, missing atoms, and nonstandard residues, are colored orange, red, green, or blue. The 1ett structure consists of two protein chains and some water molecules, all colored light gray, and a single ligand, 4-TAPAP, shown in orange. Orange indicates anything that is not a standard amino acid residue, such as a ligand, cofactor, or metal ion.

In this structure, correction of the protein structure is unnecessary, since only the ligand is a nonstandard residue. However, when you work with other proteins, you may want to investigate and manually adjust marked portions. See the Maestro online help topic on PDB conversion for more information.

In the terminal window where Maestro was started, you may see these messages:

```
WARNING check_residue: no template for residue 1 (TOS ), chain 'T'.
WARNING check_residue: no template for residue 2 (PAP ), chain 'T'.
WARNING check_residue: no template for residue 3 (PIP ), chain 'T'.
```

The ligand 4-TAPAP comprises three PDB HET groups: p-toluene sulfonate (TOS), amidophenylalanine (PAP), and piperidine (PIP). None of these is a standard amino acid residue, which means that there is no standard *connection template* to supply information about bond order or formal charges. Without this information, Maestro creates a ligand structure using only single bonds (and assigns no formal charges), which is far from correct for 4-TAPAP. The ligand structure must be corrected before it can be used in Glide and other FirstDiscovery applications. Correction of the ligand is covered in Section 3.5.

## 3.4 Deleting Unwanted Waters

There are hundreds of water oxygen atoms in this structure, as there are in most PDB structures. Because water molecules vary in relevance to the binding mode of interest, the Protein Preparation workflow allows you to decide in each case whether to keep all water molecules, delete some, or delete all.

If cocrystallized water molecules are coordinated to metal ions or are forming hydrogen-bond bridges between the ligand and protein, and you want to search for ligands that bind in the same manner as the cocrystallized ligand, you should keep those waters. (After adding hydrogens to such waters, you should orient them appropriately to facilitate receptor-ligand contacts. See Section 4.9 of the *Glide User Manual* for more information.) However, if you intend to search for ligands that might displace one or more waters, you should delete some or all of the water molecules.

For 1ETT, it is reasonable to delete all water molecules:

- Choose Waters from the Delete button menu on the toolbar.

  

  The water molecules are deleted.

## 3.5 Adjusting the Ligand

The ligand has been represented without bond order or formal charge information. This information must be added. In this exercise you will display only the ligand, then adjust its bond orders and formal charges.

### 3.5.1 Displaying Only the Ligand

It is convenient to display only the ligand while adjusting bond orders and formal charges. For most ligands and cofactors, you can do this by choosing Protein Backbone then choosing Protein Side Chains from the Undisplay button menu:

The 4-TAPAP ligand is an exception. Maestro recognizes amidophenylalanine (PAP) as an amino acid residue, although a nonstandard one, and therefore includes it when it undisplays the Protein Backbone and Protein Side Chains. To display this ligand completely you must use a different technique:

1. Choose Select from the Display only button menu in the toolbar.

   

   The Atom Selection dialog box opens, titled Select To Display Only.

2. Click the Residue tab and select Residue Type.
3. In the Residue Type list, select PAP.

   PAP, PIP, and TOS are at the end of the list because they are not standard residues. In the Workspace, the PAP residue is marked in magenta.

4. Shift-click on TOS.

   All three ligands are selected, and the entire ligand is now marked in magenta.

5. Click the Add button.

   The Atom Specification Language (ASL) expression for your selection appears in the ASL text box, and the ligand is marked in cyan.

6. Click Create Set and type the set name `4-TAPAP`, then click OK.

   This makes future references to the ligand simpler.

7. Click OK.

   The Atom Selection dialog box closes. Only the ligand appears in the Workspace.

8. Click the Fit to screen toolbar button to get a closer look at the ligand.

   

9. Choose Element from the Color all atoms by scheme button menu in the toolbar.

   

10. Choose PDB Atom Name from the Label atoms button menu.

    

    The 4-TAPAP ligand is displayed in the Workspace as shown in Figure 3.1.

An alternative procedure, which relies on the numbering of the molecules in the complex, is as follows:

1. Choose Molecules from the Display only selected atoms button menu on the toolbar.

   

2. Click on an atom in the ligand molecule.

   The ligand is displayed and the receptor is undisplayed.

You can then proceed from Step 8, above.

### 3.5.2 Adjusting Bond Orders and Formal Charges

The Workspace structure has single bonds only. Ten of these bonds need to be made double. Two procedures are presented here. The first involves manual correction of the bond orders; the second uses the Assign Bond Orders tool. This tool corrects the bond orders in most but not all cases, so you should always check your structure carefully after using it.

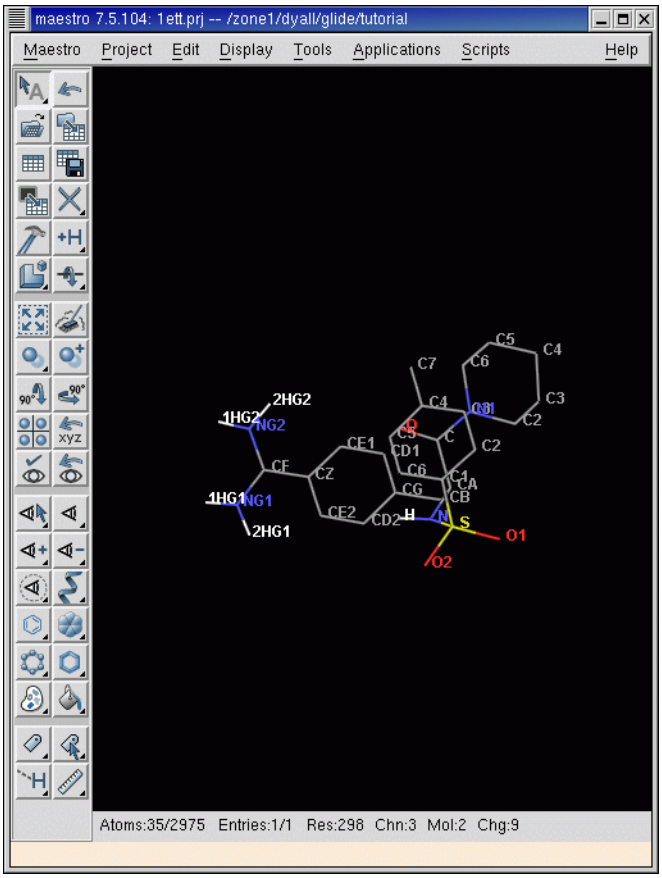


*Figure 3.1. The 4-TAPAP ligand before adjustment*

In this exercise you will need to use the Build panel, so you should open it before starting, by clicking the Open/Close Build panel button on the toolbar.

When you have finished this section, you can close the Build panel.

If you want to perform both procedures, you can export the structure and reimport it for the second procedure. To export the structure:

a. Choose Export Structures from the Project menu.

b. Enter a name such as `1ett_save` in the File text box.

c. Click Export.

**To assign bond orders manually:**

1. In the Build panel toolbar, click the Increment bond order button.

   

   The TOS residue and the PAP residue each include a six-carbon ring that is planar and therefore must be a phenyl ring (see Figure 3.1 on page 36).

2. Click on every second bond in each of the phenyl rings to increment it to a double bond.
3. Click on the two S–O single bonds to make them double bonds as well.
4. Double the C–O single bond.
5. Double the CF–NG1 bond in the PAP residue.

   The double bond is displayed, but Maestro removes a hydrogen from the double-bonded nitrogen to maintain neutrality. The charge on this nitrogen atom needs to be adjusted.

6. Click Increment formal charge on the Build panel toolbar.

   

7. Click the CF=NG1 nitrogen.
8. On the main toolbar, choose Delete Labels from the Label atoms button menu.

   

9. On the Build panel toolbar, click Label heteroatoms.

   

   Heteroatoms are labeled with their element symbol. The C=N nitrogen is also labeled with a plus sign (+) representing its formal charge of +1. The additional hydrogen on that atom will be added automatically in the preparation job.

   The structure as it appears now is shown in Figure 3.2.

The alternative procedure uses the Assign Bond Orders tool. If you have already assigned bond orders manually, re-import the complex, remove the waters and display only the ligand before proceeding with the steps below. If you saved the complex before assigning bond orders, re-import it now. The first two steps below change the labels on the ligand.

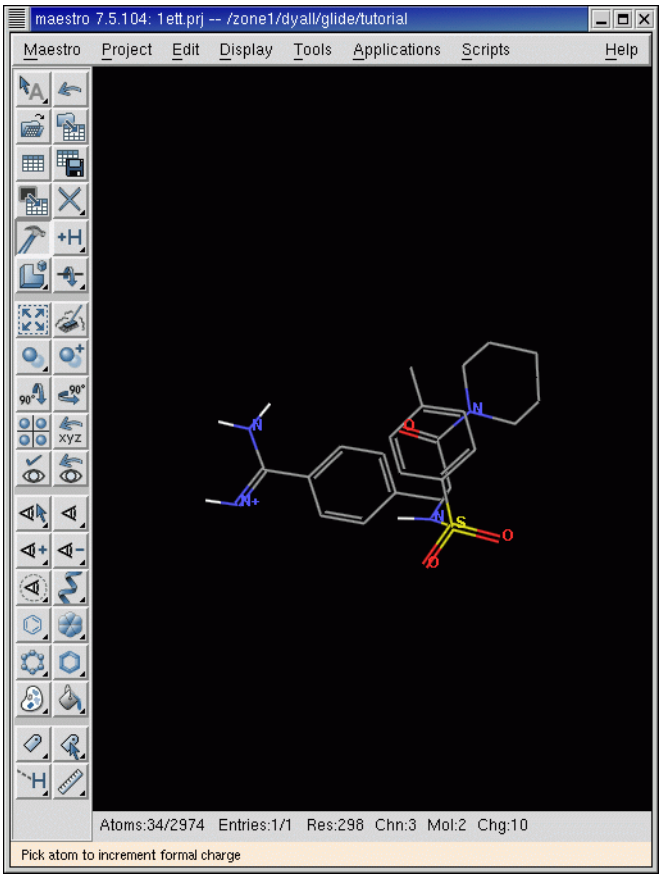


*Figure 3.2. The 4-TAPAP ligand after manual adjustment*

**To assign bond orders automatically:**

1. Choose Labels from the Delete button menu on the main toolbar.

2. On the Build panel toolbar, click Label heteroatoms.

This step labels non-carbon atoms with their element symbol and formal charge, so you can see when the charge is changed. Information on an atom, such as residue name, PDB atom name, and so on, is displayed in the status bar by pausing the pointer over the atom.

3. From the Tools menu in the main window, choose Assign Bond Orders.

   After a short delay, the bond orders are changed. Check them carefully to ensure that they are correct. The guanidine hydrogens are all retained, so the structure does not look exactly the same as in Figure 3.2.

## 3.6 Running Protein Preparation on the Structure

1. From the Glide submenu of the Maestro Applications menu, choose Protein Preparation.

   The Protein Preparation panel opens. Pick ligand and Show markers are selected by default.

2. Click an atom in the ligand.

   The ligand is marked in dark green.

Anything in the complex structure that was not selected as the ligand is treated as part of the receptor. This would include any cofactors, metals, or other ligands, if any were present.

Protein Preparation requires both ligand and receptor to be included in the Workspace. The entire 1ett structure is included in the Workspace, although only the ligand is displayed.

3. In the Procedure section, ensure that Preparation and refinement, the default, is selected.

   Each step can be run independently using the Preparation only or Refinement only options.

4. Select On under Neutralization zone around the ligand.

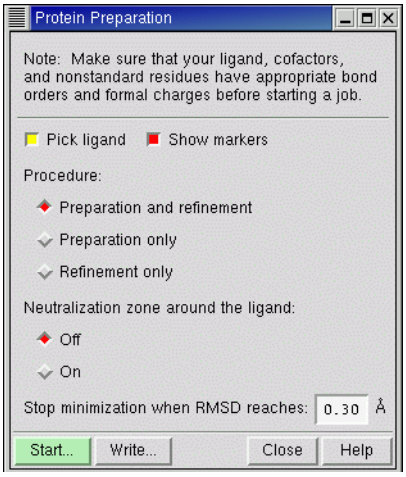


***Figure 3.3. The** Protein Preparation **panel.***

5. Ensure that the value in the Stop minimization when RMSD reaches text box is 0.30 Å

   This default value allows the refinement portion of the job to halt when the average RMSD of the heavy atoms reaches 0.30 Å.

6. Click Start.

   The Protein Preparation - Start dialog box opens.

7. Change the Job Name to `1ett_pprep`.

8. Choose a host for the job from the Host option menu.

   If you use a different user name on the remote host you have selected, enter that user name in the Username text box.

9. Click Start.

   The Monitor panel is displayed, and the preparation stage begins.

During the preparation stage, hydrogen treatment is applied to the ligand and the protein. Residues within 10–20 Å of the ligand are neutralized, which may involve conformation changes to some residues.

When preparation is finished, refinement begins. The refinement portion of the job performs a series of restrained partial minimizations of the cocrystallized complex to optimize the positions of the newly added hydrogens and relieve any strain due to unphysically short distances in the X-ray structure.

The `1ett_pprep` preparation and refinement job takes about 15 minutes on a 1GHz Pentium processor. The time required for other Protein Preparation jobs depends on the size of the protein and the procedure and settings chosen.

Instead of starting the job immediately, you can click the Write button in the Protein Preparation panel, then run the job from the command line using the `$SCHRODINGER/protprep` command. The `protprep` application has options that allow fine control over the refinement section of the procedure—see Section 8.3 of the *Glide User Manual* for details.

## 3.7 Output Structures and Files

Once the `1ett_pprep` job has run, the refined receptor-ligand complex structure in the `1ett_pprep_prot_ref.mae` file is incorporated as a new entry in the Project Table and included in the Workspace.

The receptor is still undisplayed, allowing you to inspect the ligand. Hydrogens on carbon are now explicit, a hydrogen has been added to the protonated nitrogen, and the guanidine group is planar—see Figure 3.4.

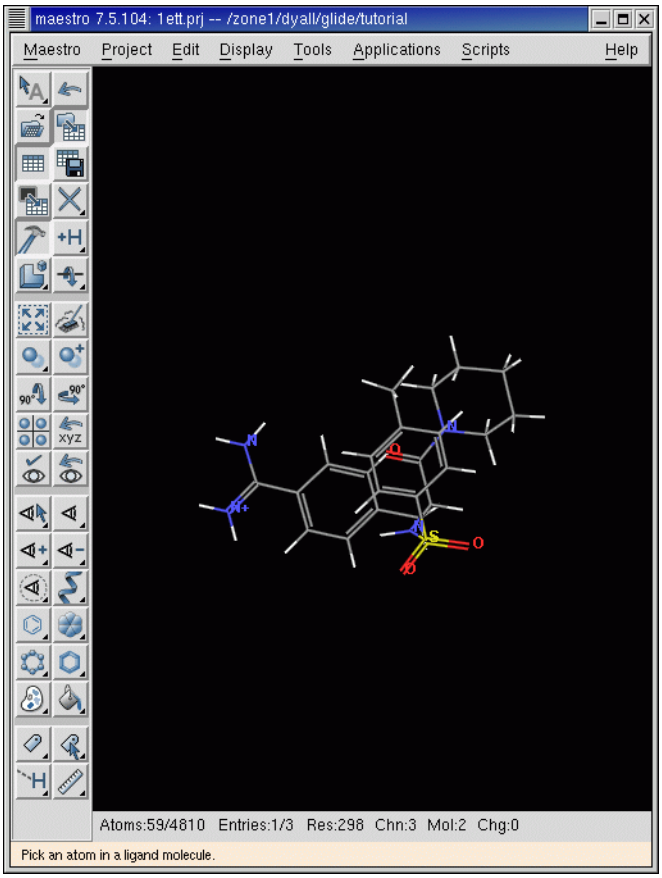


***Figure 3.4. The 4-TAPAP ligand after protein preparation***

Examine the entire prepared, refined protein-ligand complex in the Workspace:

1. Choose Molecule Number (Carbons) from the Color all atoms by scheme button menu.

   

2. Redisplay the receptor by choosing All from the Display only button menu.

   

   The receptor is displayed with carbons colored cyan, the ligand carbons are colored coral.

Export the Workspace structure to a new file for later use:

1. Choose Export Structures from the Project menu.

   The Export panel is displayed.

2. In the File text box, type the name `1ett_complex`.

3. Click Export.

   The file `1ett_complex.mae` is created. Its full path name is shown in the File text box.

In the Files list, all the Maestro files in the `proteinprep` directory are listed. These include separate structure files that have been written for the ligand and the receptor as original input, as they were after the preparation stage, and as they were after the refinement stage:

| | |
|---|---|
| `1ett_pprep_lig.mae` | Ligand structure as input |
| `1ett_pprep_lig_prep.mae` | Ligand structure after preparation stage |
| `1ett_pprep_prot.mae` | Receptor structure as input |
| `1ett_pprep_prot_prep.mae` | Receptor structure after preparation stage |
| `1ett_pprep_prot_ref.mae` | Receptor-ligand complex structure after refinement |
| `1ett_pprep.log` | The log file for the complete preparation and refinement job |

4. Close the Export panel.

In practice, after protein preparation of a raw PDB structure is complete, it is a good idea to import the output ligand and receptor structure files into Maestro for closer examination. Such an examination would include checking for obvious structural problems, ensuring that ligands and cofactors were properly hydrogen-treated, that any added formal charges remained correct, and that the structures look properly minimized. If you find any problems, correct them in the input complex structure and then run the appropriate preparation or refinement jobs again.

# Receptor Grid Generation

This chapter contains exercises that demonstrate how to use the Receptor Grid Generation panel to set up and start a grid file calculation job. Grid files represent physical properties of a volume of the receptor, specifically the active site, that will be searched when attempting to dock a ligand. You will use the grid files calculated in this chapter to dock ligands in later Glide exercises.

## 4.1 Starting Maestro

Before you begin the exercises shown below, you must first create a local tutorial directory tree, as described in Section 1.3. If you have not yet set up your tutorial directory tree, do so now, then proceed with the instructions in the appropriate section below.

If you are continuing from the previous chapter with an open Maestro session:

1. If the Commands text box is not displayed in the Maestro main window, select Command Input Area from the Display menu.
2. Type `cd ../grids` in the Commands text box.

   Maestro changes the current working directory to *yourpath*`/tutorial/grids`. The directory is displayed in the Maestro title bar.
3. Undisplay the Command Input Area.

If you are starting a new Maestro session:

1. In a terminal window, navigate to the *yourpath*`/tutorial/grids` directory you created.
2. Start Maestro. (If you have not started Maestro before, see Section 1.4.)

## 4.2 Importing the Prepared Complex

1. Click the Import structures button on the toolbar.

   

   The Import panel is displayed.

2. Ensure that Maestro is selected from the Format menu.
3. Ensure that Import all structures is selected.
4. Ensure that First Imported Structure is selected from the Include in workspace menu.
5. Select the file `1ett_complex.mae`:
   - If you created a `1ett_complex.mae` file in Chapter 3, navigate to your `proteinprep` directory and select the file.
   - If you did not create a `1ett_complex.mae` file, navigate to your `structures` directory and select the file.
6. Click Import.

   The prepared complex is displayed in the Workspace. The ligand is visible in a contrasting color. Hydrogens are shown.

## 4.3 Defining the Receptor

Before calculating receptor grids for a cocrystallized ligand-receptor complex, you need to exclude the ligand atoms from consideration:

1. Choose Receptor Grid Generation from the Glide submenu of the Applications menu in the main window.

   The Receptor Grid Generation panel opens with the Receptor tab displayed.

2. In the Define receptor section, ensure that the Pick to identify ligand molecule option and the Show markers option are selected.
3. In the Workspace, pick an atom in the ligand molecule.

   The ligand molecule carbons are colored differently from the receptor carbons. Dark green markers appear on the ligand.

4. In the Van der Waals radii scaling section, ensure that Scale by is set to the default value of 1.00 (no scaling.)

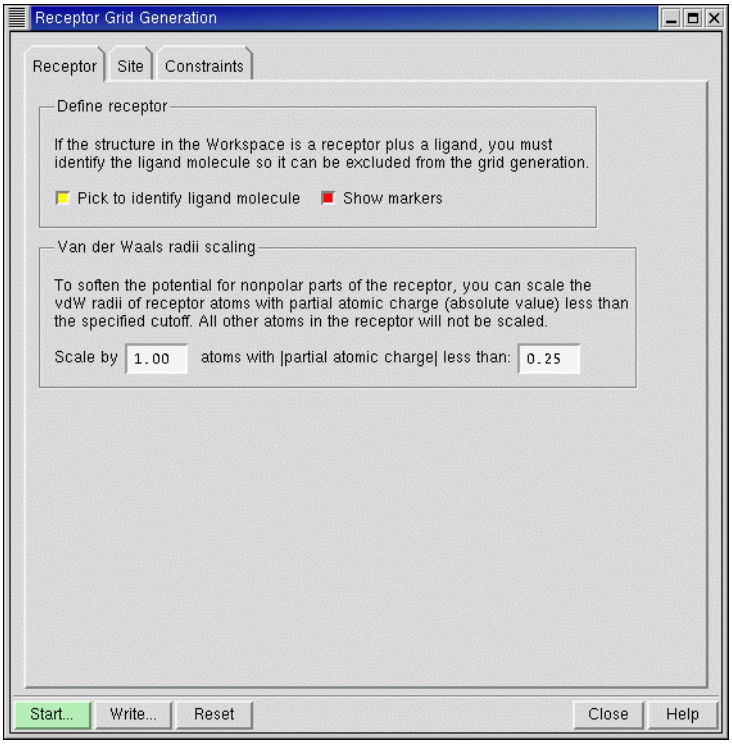


***Figure 4.1. The*** Receptor Grid Generation ***panel.***

## 4.4 Defining the Active Site

Now that the ligand has been excluded, the volume for which grids will be calculated can be defined:

1. Click the Site tab.

   The entire complex is shown with several types of markers: the dark green ligand molecule markers that appeared when the ligand was identified, and the new markers that appeared when the Site tab was opened:

   - The *enclosing box* is shown in purple.
   - The center of the enclosing box is marked by green coordinate axes.

   The purple enclosing box represents the volume of the protein for which grids will be calculated. Generally, you should make the enclosing box as small as is consistent with the shape and character of the protein's active site and with the ligands you expect to dock.

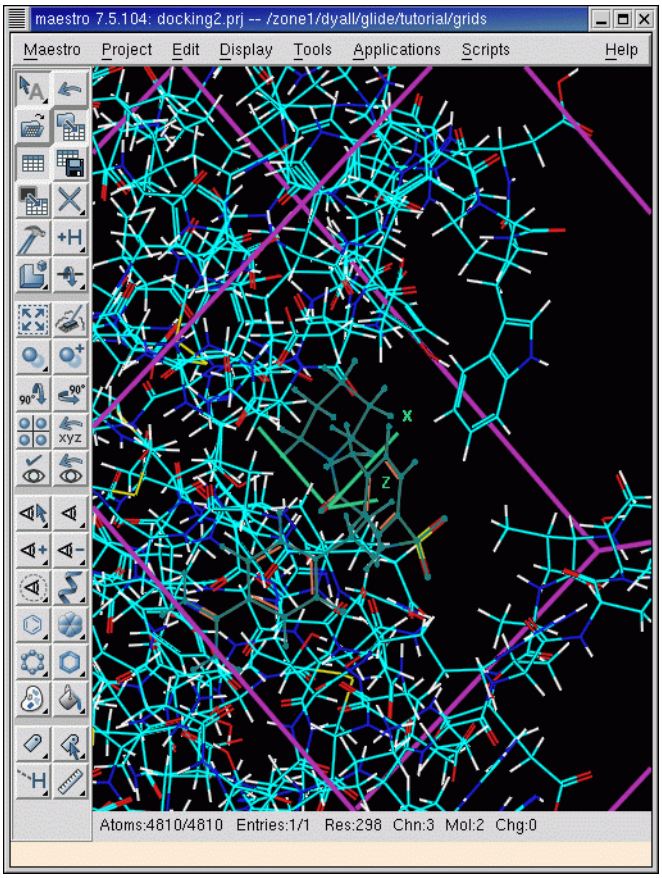


***Figure 4.2. The marked ligand with enclosing box.***

2. In the Site tab, ensure that the Center option selected is Centroid of Workspace ligand.
3. Ensure that the Size option selected is the default, Dock ligands similar in size to the Workspace ligand.

   If you have a representative ligand in the active site, the default generates an enclosing box that is large enough for most systems. However, if you think that conformations of active ligands may exist that are significantly larger than the cocrystallized ligand, you should consider enlarging the enclosing box using the Dock ligands with length <= option.

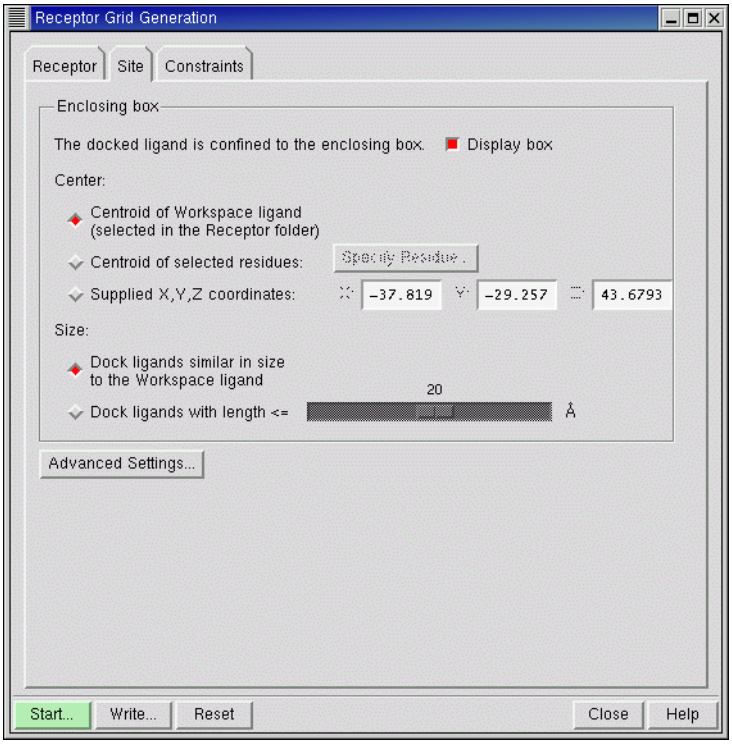


***Figure 4.3. The** Site **tab of the** Receptor Grid Generation **panel.***

## 4.5 Setting Up Glide Constraints

The Constraints tab of the Receptor Grid Generation panel is used to define Glide constraints. In this exercise, you will define three constraints: a positional constraint, an H-bond constraint, and a hydrophobic constraint. To make it easier to see the parts of the receptor close to the ligand and to see the ligand atoms, you will first change the display.

For more information on using Glide constraints, see Section 6.4 of the *Glide User Manual*.

### 4.5.1 Setting the Display for Constraint Definition

1. Choose Molecules from the Display only selected atoms button menu, and click on a ligand atom.

   

   The ligand is displayed, and the receptor is undisplayed.

2. Choose Molecules from the Draw atoms in Ball & Stick button menu, and click on a ligand atom.

The ligand is displayed in Ball & Stick representation, and the dark green markers change to cubic outlines.

3. Choose 3 Å from the Display residues within N Å of currently displayed atoms button menu.

The residues that are closest to the ligand are displayed.

### 4.5.2 Defining a Positional Constraint

1. In the Constraints tab, click the Positional tab.
2. Click New.

   The New Position dialog box opens.

3. Ensure that Pick is selected in the Select atoms to define a position section, and that Atoms is selected from the Pick option menu.
4. Click the sulfur atom of the sulfone group in the Workspace.

   A gray sphere is displayed around the atom.

5. Enter the name `pos_sulfone` in the Name text box.
6. Ensure that the radius is 1.00.

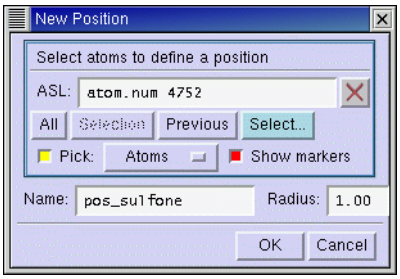


***Figure 4.4. The** New Position **dialog box.***

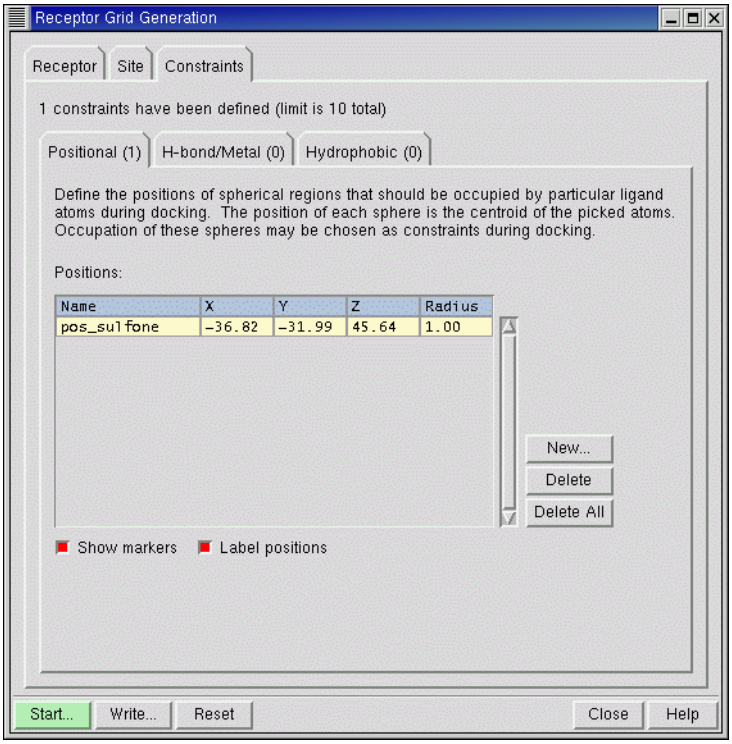


***Figure 4.5. The*** Constraints ***tab of the*** Receptor Grid Generation ***panel showing the*** Positional ***subtab.***

7. Click OK.

   The constraint is added to the Positions table in the Positional tab, and the sphere changes to yellow. The name is displayed next to the sphere.

### 4.5.3 Defining an H-bond Constraint

Next, you will define an H-bond constraint, for the carboxylate that is hydrogen-bonded to the amidine of the ligand. To facilitate the picking of the constraint, H-bonds to the ligand will be displayed.

1. Choose Inter H-bonds from the Display H-bonds button menu, and click on a ligand atom.

   

   The hydrogen bonds between the ligand and the receptor are displayed as yellow dashed lines.

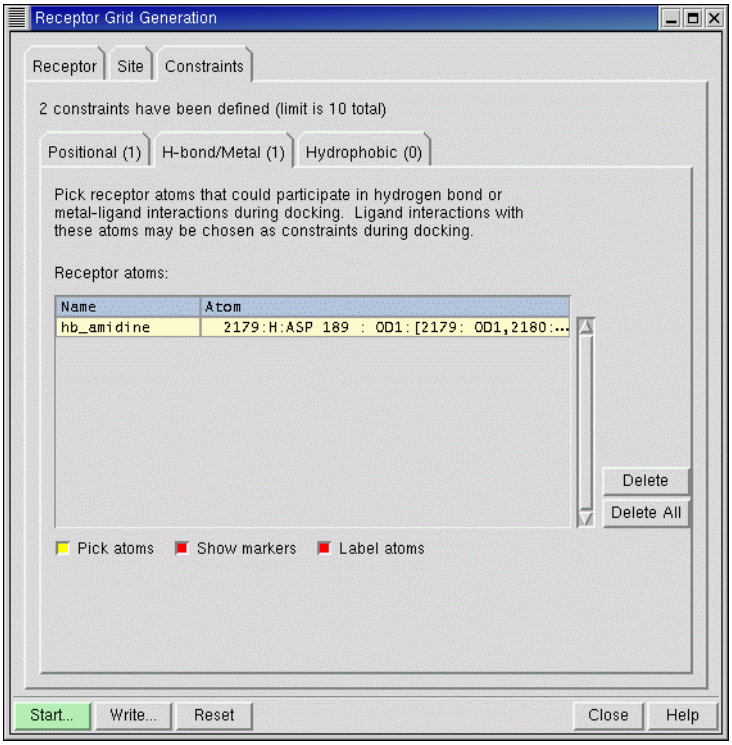


***Figure 4.6. The*** Constraints ***tab of the*** Receptor Grid Generation ***panel showing the*** H-bond/Metal ***subtab.***

2. In the H-bond/Metal subtab of the Constraints tab, select Pick atoms, then click on the carboxylate oxygen that is hydrogen-bonded to the amidine of the ligand.

   This atom is the OD1 atom of ASP 189. You can check this by pausing the pointer over the atom. Information on the atom is displayed in the Workspace status area.

   When you have picked the atom, an entry is added to the Receptor atoms table. In the Atom column, both oxygen atoms of the carboxylate are listed in square brackets, because Glide includes symmetry-related atoms as part of the constraint. Both atoms are marked in the Workspace with a padlock icon, if Show markers is selected, and the name is also displayed if Label atoms is selected.

3. Name the constraint `hb_amidine`, by editing the text in the Name column.

4. Choose Delete H-bonds from the Display H-bonds button menu.

### 4.5.4 Defining a Hydrophobic Constraint

Hydrophobic constraints are defined from data generated by a SiteMap calculation. The hydrophobic regions are displayed as a set of cubes, which you can add to a hydrophobic constraint region. This region must be occupied by hydrophobic ligand atoms when you dock ligands.

1. In the Hydrophobic subtab of the Constraints tab, click Locate Hydrophobic Cells.

   A SiteMap job is started. The octagon to the right of this button turns green and spins while the job is running. The job takes a few minutes. When it finishes, gray cubes ("hydrophobic cells") are displayed in the Workspace, and a default region is added to the table in the Define regions section.

   One hydrophobic region is near the benzene ring to which the amidine is attached. The other is an extended region that covers part of the piperidine and part of the tolyl group attached to the sulfone. We will select the region that includes the methyl group.

2. Select Pick to add/remove cells in the Define regions section.

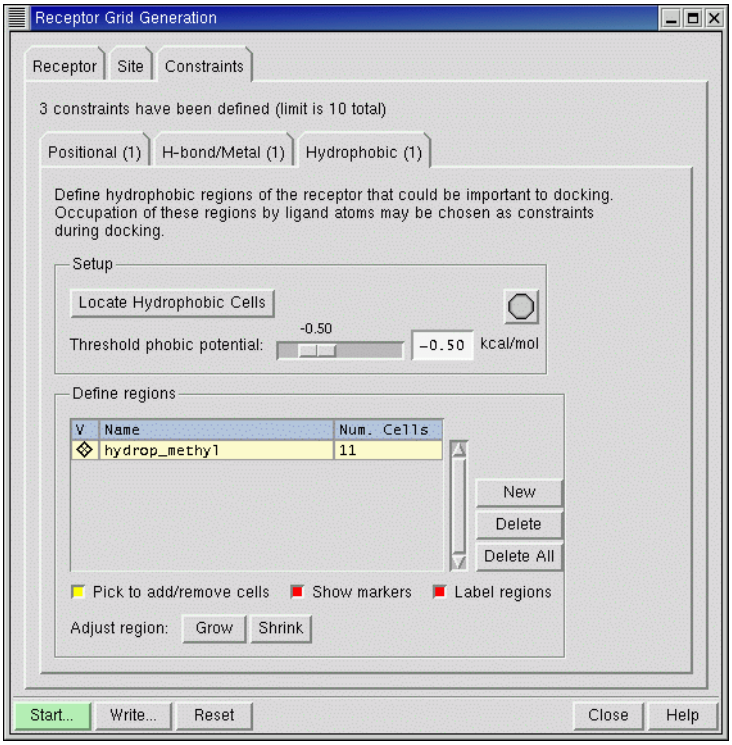


***Figure 4.7. The*** Constraints ***tab of the*** Receptor Grid Generation ***panel showing the*** Hydrophobic ***subtab.***

3. Click on the cell near the methyl group that has the largest *y* and *z* coordinates (not the cell on its own some distance away).

   You might need to rotate the structure to see this cell, and also to undisplay the receptor. When you click it, the cell turns red and is outlined in yellow. The default name, region1, is displayed next to it.

4. Click Grow twice.

   For each click, the cells adjacent to the red cells are added to the region. After the second click, the value in the Num Cells column should be 11.

5. Change the name of the region to `hydrop_methyl` by editing the text in the Name column.

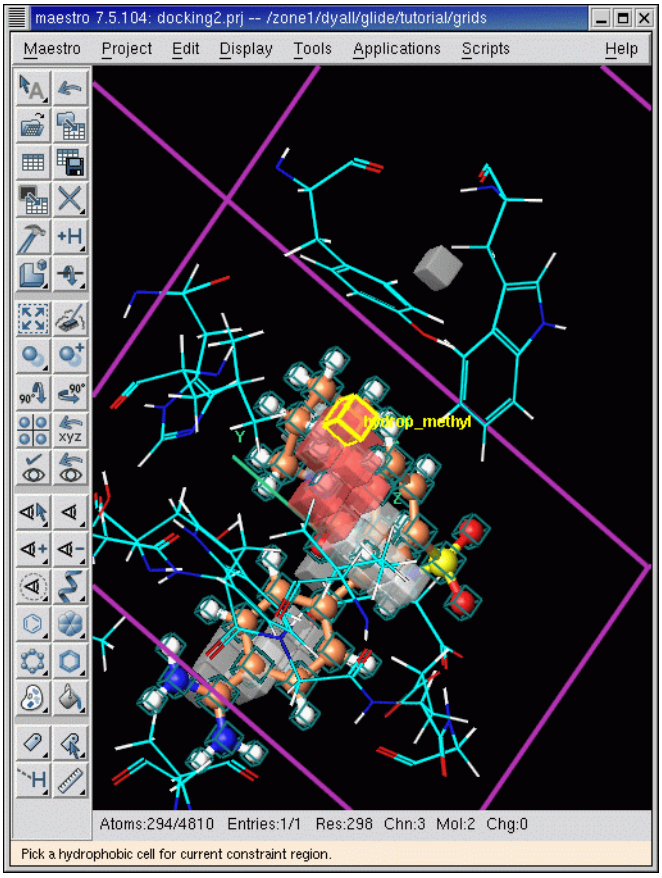


***Figure 4.8. Hydrophobic constraint cells with a selected region.***

## 4.6 Starting and Monitoring the Grid Calculation

With the ligand and the active site defined, and constraints set up, the grid generation job can be started.

1. Click the Start button in the lower left corner of the Receptor Grid Generation panel.

   The Receptor Grid Generation - Start dialog box is displayed.

2. In the Output section, ensure that the Directory for grid files is the default, `./` , your current working directory.

3. Check the main window title bar to confirm that the current working directory is *yourpath*`/tutorial/grids`.

4. In the Job section, change the Name to `1ett_grids`.

5. Choose a host and, if necessary, specify a user name.

6. Start the job by clicking Start.

   After a moment, the Monitor panel is displayed. The job starts.

While the job is in progress, the panel's Status column displays the word "running." When the job is complete, the status is changed to "Incorporated : finished".

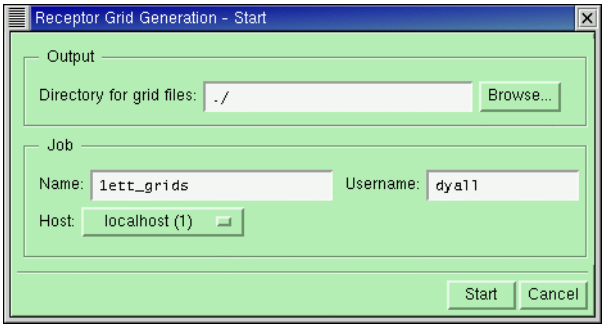


***Figure 4.9. The*** Receptor Grid Generation - Start ***dialog box.***

You can also start, monitor, and interrupt Glide jobs from the command line. For more information, see Chapter 5 of the *Job Control Guide*.

The job takes approximately 10 minutes on a 1 GHz Pentium 4 processor; this time may vary depending on your particular system configuration and workload.

Before the job is launched, these job input files are written:

| | |
|---|---|
| `1ett_grids.inp` | Command input for grids job |
| `1ett_grids.mae` | Receptor structure input for grids job |

When the calculation is complete, the `grids` directory will contain job output files:

| | |
|---|---|
| `1ett_grids.log` | Log summary file from grids job |
| `1ett_grids.out` | Output summary file from grids job |

It will also contain many grid files. You will not need to deal with these files individually, only as a group represented by `1ett_grids.grd`:

| | | |
|---|---|---|
| `1ett_grids.cons` | `1ett_grids_coul2.fld` | `1ett_grids.csc` |
| `1ett_grids.grd` | `1ett_grids_greedy.save` | `1ett_grids.gsc` |
| `1ett_grids.phob` | `1ett_grids_recep.mae` | `1ett_grids.save` |
| `1ett_grids.site` | `1ett_grids_vdw.fld` | |

When you set up the ligand docking job, you will need to type the receptor grid base name (directory and job name) for these files (*yourpath*`/tutorial/grids/1ett_grids`) or browse for the file `1ett_grids.grd` (the browse filter in this step is automatically set to `*.grd`). A new job name for each grid calculation is helpful.

In the next chapter, you will dock ligands using these grids.

# Ligand Docking

The exercises in this chapter demonstrate the use of Glide to screen a multiple-ligand file for structures that interact favorably with a receptor active site. The receptor grid files you calculated in the previous chapter will be used to dock ligands from the file `50lig.mae`. Most of the 50 ligands in the file are decoys, selected as a representative sample from a database of drug-like molecules using the `ligparse` utility. Four ligands out of the total of 50 are active ligands of bovine thrombin from PDB structures, including the `1ett` native ligand 4-TAPAP. Typically, Glide standard-precision docking is used to find probable good binders in a large set; the top-scoring 10% to 30% can then be investigated more intensively using Glide extra-precision (XP) docking or other methods available from Schrödinger.

## 5.1 Preparation

If you are continuing from the previous exercise, you must ensure that the current working directory is correct. If you are starting the exercises at this point, you must copy the relevant files first.

If you have completed the exercises in Chapter 4 and have a Maestro session open:

1. If the Commands text box is not displayed in the Maestro main window, select Command Input Area from the Display menu.
2. Type `cd` *yourpath*`/tutorial/glide` in the Commands text box.

   If you are continuing directly from Chapter 4 you can type `cd ../glide` instead.

   Maestro changes the current working directory to *yourpath*`/tutorial/glide`. This is the directory you will use for the docking files you create in this chapter.
3. Undisplay the Command Input Area.

If you have completed the exercises in Chapter 4 but Maestro is not running:

1. In a terminal window, change directory to *yourpath*`/tutorial/glide`.

   This is the directory you will use for the docking files you create in this chapter.
2. Start Maestro.

If you are starting the tutorial with this chapter and have not yet set up your tutorial directory tree, do so as described in Section 1.3. Then follow the instructions below.

1. Copy the `1ett_grids.*` grid files from `$SCHRODINGER/impact-v`*version*`/tutorial/grids` to your local *yourpath*`/tutorial/grids` directory.
2. In a terminal window, change directory to *yourpath*`/tutorial/glide`.
3. If Maestro is not running, start Maestro. If Maestro is running, follow the instructions above for continuing with a Maestro session.

   If you have not started Maestro before, see Section 1.4.

## 5.2 Specifying a Set of Grid Files and Basic Options

In this section, you specify that the grid files you calculated in Chapter 4 be used for the ligand docking job that will be run in this chapter.

1. Click the Clear workspace toolbar button.

   

2. Choose Ligand Docking from the Glide submenu of the Applications menu.

   The Ligand Docking panel opens with the Settings tab displayed.

3. In the Receptor grid section, click the Browse button.

   A file selector opens.

4. Navigate to the *yourpath*`/tutorial/grids` directory, choose `1ett_grids.grd`, and click OK.

   The Receptor grid base name is *yourpath*`/tutorial/grids/1ett_grids`.

5. In the Docking section, ensure that the Precision option is SP (standard precision).

   This is usually the best choice for docking large numbers of ligands. For more rapid screening you can use the HTVS (high throughput virtual screening) option. You will do this in a later exercise.

6. Under Options, ensure that Dock flexibly and Allow flips of 5- and 6-member rings are selected, and Allow is chosen from the Twisted (nonplanar) amide bonds option menu.

7. In the Similarity tab, ensure that the Mode is set to the default, Do not use similarity.

   For information about using Glide similarity, see the online help and Section 7.5 of the *Glide User Manual*.

The receptor grids and the basic Glide settings for the ligand docking job are now specified. In the next section, you will specify a set of ligands to dock.

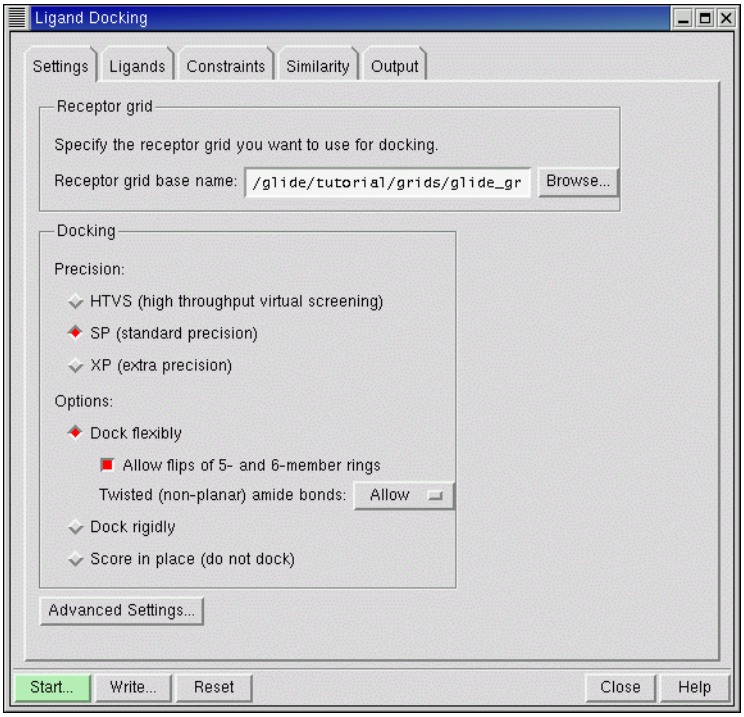


***Figure 5.1. The** Settings **tab of the** Ligand Docking **panel.***

## 5.3 Specifying Ligands To Dock

There are several methods for specifying ligand structures to be docked with receptor grids. In this tutorial, you will specify a file containing a set of 50 ligands.

1. In the Ligands tab, ensure that From file is selected and that File format is set to Maestro.
2. Click Browse.

   A file selector is displayed.
3. Navigate to the *yourpath*`/tutorial/structures` directory, choose `50lig.mae`, and click OK.
4. Ensure that the selected Range is from `1` to End (the default).
5. Ensure that van der Waals radii scaling for ligand atoms is set to the default values: Scale by `0.80` atoms with |partial atomic charge| less than `0.15`.

In this docking job the constraints that were specified in the grid generation will not be used. In a later exercise you will use the constraints to dock the same ligands.

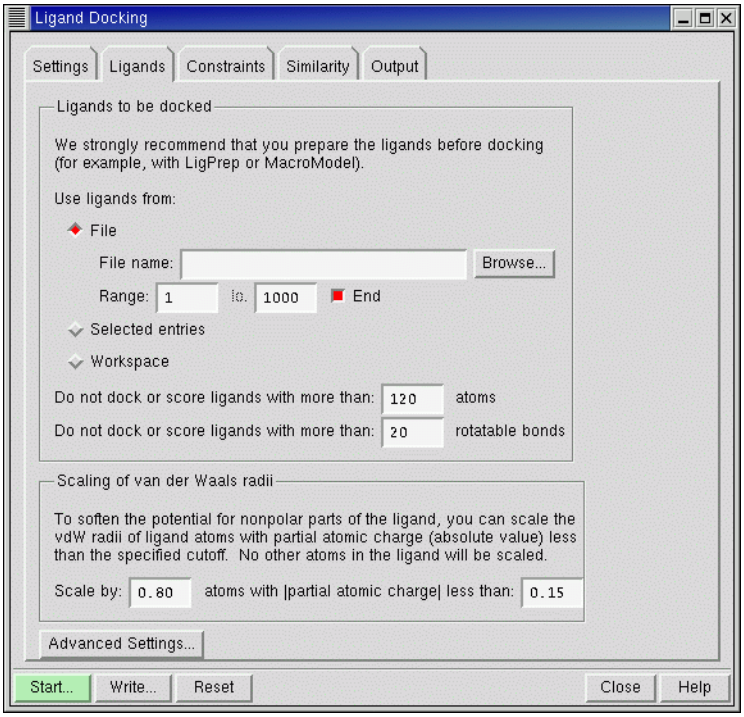


***Figure 5.2. The** Ligands **tab of the** Ligand Docking **panel.***

## 5.4 Specifying Output Quantity and File Type

Use this tab to specify the type of file to create for the output ligand poses and to determine how many poses to write, per ligand and per docking job.

1. In the Structure output section of the Output tab, ensure that Write pose viewer file (includes receptor; filename will be <jobname>_pv.mae) is selected.

   You are specifying that the structural output from the docking job be written to a pose viewer file, a file of ligand poses that begins with the structure of the receptor. Having the receptor structure included in the file is convenient for displaying contacts between the ligand and the receptor. In Chapter 6, you will use the Pose Viewer panel to examine the poses in the file `1ett_dock_pv.mae`.

2. Ensure that the value of *m* in the Write out at most *m* poses per ligand text box is 1, the default.

   Because there are only 50 ligands in the input file, this setting ensures that no more than 50 poses, one for each ligand, will be collected and written to the pose viewer file.

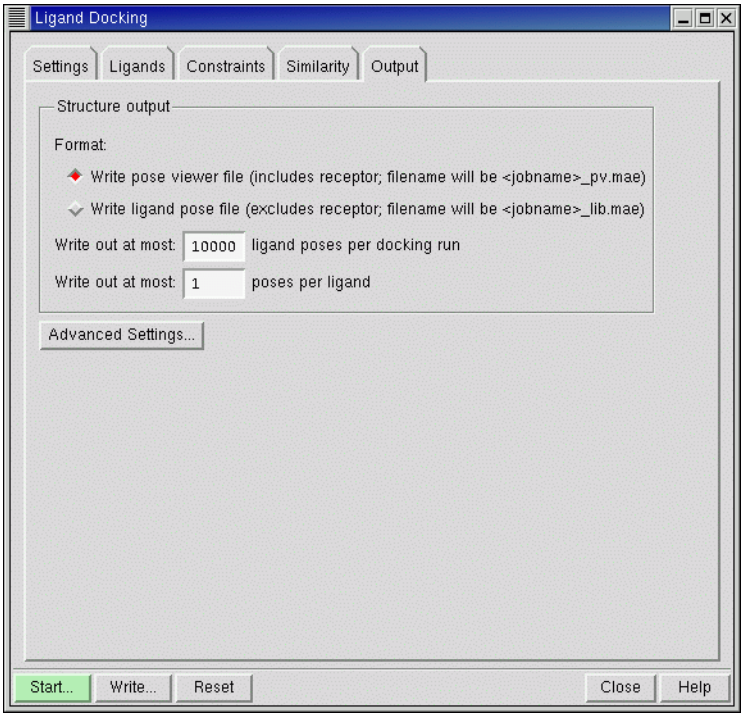


***Figure 5.3. The*** Output ***tab of the*** Ligand Docking ***panel.***

## 5.5 Setting Up Distributed Processing

If you have access to a host machine with multiple CPUs, the `para_glide` application can divide your multiple-ligand docking job into subjobs that can be distributed over several processors. Options in the Ligand Docking - Start dialog box allow you to specify the number of subjobs and the number of processors to use. (For more on command-line `para_glide`, see Section 8.5 of the *Glide User Manual*.) In this section, it is assumed that a host with multiple processors is available. If you have access to a host with five or more processors, and you can use five of its processors for this docking job, you can follow the instructions in this section without alteration. If the host has fewer than five processors, or you do not want to use five of its processors for this job, change the settings below accordingly.

If you cannot, or do not want to, distribute processing over multiple CPUs, skip to Section 5.6.

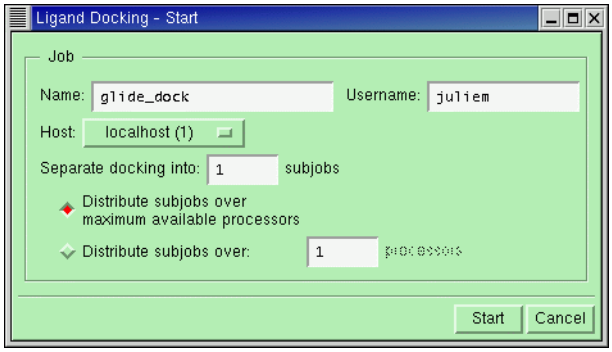


***Figure 5.4. The** Ligand Docking - Start **dialog box, default settings.***

1. Click Start.

   The Ligand Docking - Start dialog box opens.

2. Choose a multiple-processor host from the Host option menu.

   In this example, the host selected has eight processors.

3. If you have a different user name on the host you have selected than on your local host, enter the correct user name in the Username text box.

4. Change the value in the Separate docking into *j* subjobs text box to 10.

   The docking job will be split into 10 subjobs, each one docking 5 ligands. For the sake of speed, the number of ligands per subjob in this exercise is much smaller than would be typical in actual use. The default for *j* is 1, meaning that the job is run as a single job.

By default, the option Distribute subjobs over maximum available processors is selected. This option distributes the subjobs to all available processors on the host. In this case, it would send one subjob to each of the eight processors in the first wave, with the last two subjobs sent to whichever processors finished fastest. However, in this example, only five processors will be used, leaving three free for other tasks.

5. Select the option Distribute subjobs over *p* processors.

   The text box becomes available.

6. Enter 5 in the text box.

   The 10 subjobs will be distributed over 5 processors. The first five subjobs will be sent first, followed by each of the remaining five as processors become available.

When you are satisfied with your distributed processing settings, continue to Section 5.6.

## 5.6 Starting the Ligand Docking Job

1. In the Ligand Docking - Start dialog box, change the Name to `1ett_dock`.
2. If you have not already done so, select a Host machine and change the Username for that machine, if necessary.
3. Click Start.

   The docking job starts and the Monitor panel is displayed.

For the distributed processing example, as soon as the `1ett_dock` job has been launched, it is divided into subjobs. As each subjob is launched on a processor, it is listed in the Monitor panel. When one subjob is finished, the next one is launched. To view the log for any subjob, select it in the job table and click Monitor. If the subjob is already finished, the entire log can be scrolled through in the text area of the Monitor panel. The results for each subjob are stored in subdirectories of the output directory, and collected at the end into the output directory.

The time required for Glide docking jobs depends on the processor speed and workload, the size and flexibility of the ligands, and the volume specified by the enclosing box. As a rough estimate, docking a typical drug-like ligand takes about one minute on a 1.2 to 1.5 GHz Pentium 4 processor under Linux, using Glide 4.0 default settings. On a similar machine with a single processor, the 50-ligand docking job will usually finish in about 45 minutes. As 10 subjobs distributed over 5 similar processors, the docking job will finish in about 15 minutes.

## 5.7 Examining the Output Files

As well as the log file (`.log`) and the output file (`.out`), the docking job generates a report file, named `1ett_dock.rept` (`1ett_dock_1_50.rept` for parallel jobs), and a pose viewer file named `1ett_dock_pv.mae` (`1ett_dock_1_50_pv.mae` for parallel jobs). In both files, ligands are arranged so that poses with the highest scores (i.e., most favorable interactions with the receptor) appear at the top. This allows you to see at a glance which of the saved ligand poses should be studied further. The report file will be briefly surveyed here; the pose viewer file will be examined in Chapter 6.

For more information on the files and their contents, see Chapter 8 of the *Glide User Manual*.

Of the 50 ligands, poses are reported for 49 ligands. To find out which ligand did not produce any poses and why, you can check the `.log` file, which reports that no good poses were found for ligand 11. Now examine the report file, by doing one of the following:

- Widen a terminal window to 180 characters and display the contents of the report file.
- Open the report file in a text editor and ensure that the lines do not wrap.

The report file is *yourpath*/tutorial/glide/1ett_dock.rept or, if you ran a parallel docking job, *yourpath*/tutorial/glide/1ett_dock_1_50.rept.

After noting how many poses were reported, and whether any poses were rejected by the energy filters, the report file presents a table of ligand poses. The highest-scoring ligands are listed first. Table 5.1 shows the first 15 ligand poses with a few of their properties. Your scores may differ slightly from those in Table 5.1; the most significant information in the .rept file is which ligands scored highest. Three of the four active ligands are ranked highest; the fourth is ranked 13th. The scores of the lower-ranked ligands are more closely spaced, so small numerical variations may result in a different order.

For distributed processing, because information is collected from the subjob directories and assembled in 1ett_dock_1_50.rept, the ligand numbers are relative to the subjob from which they were obtained, not the overall job.

*Table 5.1. The 15 highest-scoring ligand poses from* 1ett_dock.rept.

| Rank | Title | Lig# | Score | GScore |
|---|---|---|---|---|
| 1 | 1dwd | 48 | –10.58 | –10.58 |
| 2 | 1ett | 50 | –9.73 | –9.73 |
| 3 | 1etr | 49 | –8.84 | –8.84 |
| 4 | 877766 | 46 | –8.65 | –8.65 |
| 5 | 865278 | 45 | –8.55 | –8.55 |
| 6 | 334669 | 9 | –8.50 | –8.50 |
| 7 | 35 | 1 | –8.46 | –8.46 |
| 8 | 184284 | 6 | –8.22 | –8.22 |
| 9 | 504892 | 15 | –8.15 | –8.15 |
| 10 | 755486 | 34 | –8.00 | –8.00 |
| 11 | 700000 | 28 | –7.96 | –7.96 |
| 12 | 412277 | 13 | –7.89 | –7.89 |
| 13 | 1dwc | 47 | –7.79 | –7.79 |
| 14 | 151943 | 3 | –7.78 | –7.78 |
| 15 | 141500 | 2 | –7.73 | –7.73 |

## 5.8 Docking in High-Throughput Virtual Screening Mode

Glide has a set of predetermined options that can speed up the docking by a factor of about seven over the standard precision (SP) docking mode. In this exercise, you will run an HTVS docking job on the same set of ligands as used in the SP docking exercise.

1. In the Settings tab, select HTVS (high throughput virtual screening).

   The other settings will be left as they were for the SP docking job.

2. Click Start.

   The Start dialog box opens. You should not need to run this job on multiple processors.

3. Change the job name to `1ett_htvs`.

4. Select a host, and set the number of processors to 1.

5. Click Start.

   The job should take only a few minutes to run.

When the job finishes, examine the results in the report file, `1ett_htvs.rept`. Results for the top 15 ligands are shown in Table 5.2.

Of the 50 ligands, poses are reported for 46 ligands. Ligand 11 and ligand 15 produced no good poses, and poses of ligand 38 and ligand 43 were rejected in the energy filtering. The four actives are ranked 2, 3, 4, and 20. The scores are generally smaller than in SP docking.

*Table 5.2. The 15 highest-scoring ligand poses from* `1ett_htvs.rept`.

| Rank | Title | Lig# | Score | GScore |
|---|---|---|---|---|
| 1 | 877766 | 46 | –8.19 | –8.19 |
| 2 | 1dwc | 47 | –8.00 | –8.00 |
| 3 | 1etr | 49 | –7.47 | –7.47 |
| 4 | 1ett | 50 | –7.39 | –7.39 |
| 5 | 726588 | 32 | –7.36 | –7.36 |
| 6 | 716152 | 31 | –7.34 | –7.34 |
| 7 | 151943 | 3 | –7.34 | –7.34 |
| 8 | 804377 | 42 | –7.26 | –7.26 |
| 9 | 193459 | 7 | –7.13 | –7.13 |
| 10 | 290782 | 8 | –7.00 | –7.00 |
| 11 | 767637 | 36 | –6.92 | –6.92 |
| 12 | 672758 | 26 | –6.85 | –6.85 |
| 13 | 141500 | 2 | –6.56 | –6.56 |
| 14 | 755486 | 34 | –6.55 | –6.55 |
| 15 | 534167 | 17 | –6.51 | –6.51 |

## 5.9 Docking Ligands Using Constraints

In this exercise, you will apply the constraints you defined in the grid generation to the docking of the same set of ligands as for the standard SP job. By default, no constraints are applied, even if they are defined. Here, you will require any one of the three constraints to be applied.

1. In the Settings tab, select SP (standard precision).

   The other settings will be left as they were for the SP docking job.

2. In the Constraints tab, click all three check boxes in the Use column.

   These check boxes mark the constraint for use in docking.

3. Under Must match, select At least, and enter 1 in the text box.

   Of the three constraints you selected for use, this choice ensures that at least one must match for the ligand to be docked. The Total number of constraints requested shows 1, not 3, because only one of these is required.

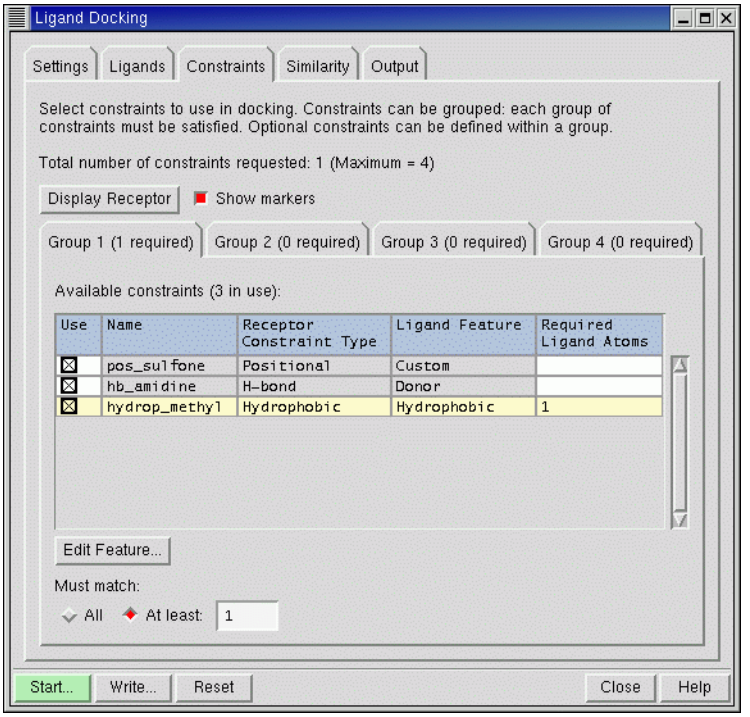


***Figure 5.5. The*** Constraints ***tab of the*** Ligand Docking ***panel.***

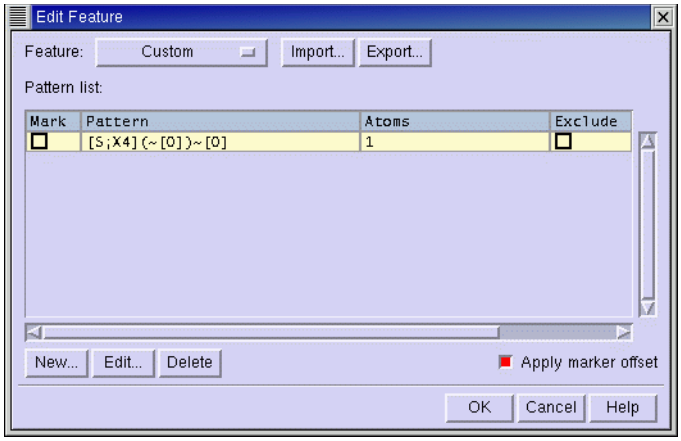


***Figure 5.6. The** Edit Feature **dialog box.***

For H-bond and hydrophobic constraints, the ligand features that must match these constraints are predefined. You can edit them if you want, but this is not necessary. For positional constraints, you must define the ligand feature that matches the constraint. Features are defined in terms of SMARTS patterns.

4. Select the pos_sulfone row in the Available constraints table, and click Edit Feature.

   The Edit Feature dialog box opens. There are no SMARTS patterns in the Pattern list table, because the Custom feature type is undefined by default.

5. Click New.

   The New Pattern dialog box opens.

6. Enter the following text into the SMARTS pattern text box:

   `[S;X4](~[O])~[O]`

   This pattern matches the sulfone functional group.

7. Enter `1` into the Numbers text box.

   This is the index of the atom in the SMARTS pattern that is matched by the constraint. Since the positional constraint was centered on the sulfur atom of the sulfone, the sulfur atom should be the one that matches.

8. Click OK.

   The New Pattern dialog box closes, and a row is added to the Pattern list table in the Edit Feature dialog box.

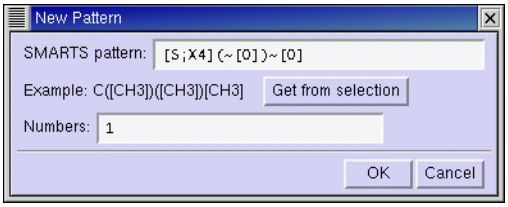


***Figure 5.7. The** New Pattern **dialog box.***

9. Click OK.

   The Edit Feature dialog box closes. This completes the definition of the Custom feature. If you did not define this feature, the docking job would not be started.

10. Click Start.

    The Start dialog box opens. If you ran the SP docking job on multiple processors before, you can do the same for this job.

11. Select the host and number of processors.

12. Change the job name to `1ett_constraints` and click Start.

    The Monitor panel opens and displays the progress of the job.

When the job finishes, examine the results in the report file, `1ett_constraints.rept`. Results for the top 15 ligands are shown in Table 5.3.

Of the 50 ligands, poses are reported for 45 ligands. Ligands 9, 11, 15, 38, and 43 did not meet the constraints. The four actives are ranked 1,2, 3, and 5. For the active ligands and one or two others, the scores are almost the same as in SP docking without constraints. For the remaining ligands, the scores are smaller (less negative), indicating that the application of constraint is serving to discriminate between ligands that bind in the proper mode, and ligands that don't.

*Table 5.3. The 15 highest-scoring ligand poses from* `1ett_constraints.rept`.

| Rank | Title | Lig# | Score | GScore |
|---|---|---|---|---|
| 1 | 1dwd | 48 | –10.61 | –10.61 |
| 2 | 1ett | 50 | –9.70 | –9.70 |
| 3 | 1etr | 49 | –8.51 | –8.51 |
| 4 | 412277 | 13 | –7.85 | –7.85 |
| 5 | 1dwc | 47 | –7.85 | –7.85 |
| 6 | 687624 | 27 | –7.74 | –7.74 |
| 7 | 644922 | 24 | –7.74 | –7.74 |
| 8 | 563036 | 19 | –7.63 | –7.63 |
| 9 | 564430 | 20 | –7.60 | –7.60 |
| 10 | 716152 | 31 | –7.30 | –7.30 |
| 11 | 865278 | 45 | –7.17 | –7.17 |
| 12 | 804377 | 42 | –7.15 | –7.15 |
| 13 | 290782 | 8 | –7.08 | –7.08 |
| 14 | 773312 | 37 | –6.96 | –6.96 |
| 15 | 672758 | 26 | –6.85 | –6.85 |

# Examining Glide Data

In this chapter, Glide results are examined with an emphasis on visual rather than numerical appraisal. The following exercises use the Glide Pose Viewer panel to display the results of a Glide docking job, examine individual ligand poses and their contacts with the input receptor structure, and write out ligand poses files to individual structure files.

These tasks can also be accomplished using features of the Project Table and the Measurements panel. See the online help or the *Maestro User Manual* for assistance.

## 6.1 Preparation

Before you start the exercises in this chapter, you should ensure that:

- Maestro is running in the *yourpath*`/tutorial/glide` directory.
- The Workspace is cleared of any structures. To clear the Workspace, click the Clear workspace toolbar button.

  

  If there are no structures in the Workspace, the Clear workspace button is not available.

If you have completed the exercises in Chapter 5 and Maestro is still running, you should already be in the *yourpath*`/tutorial/glide` directory.

If you are continuing from Chapter 5 after closing Maestro:

- Open a terminal window, change to the *yourpath*`/tutorial/glide` subdirectory, and start Maestro (see Section 1.4).

If you have not completed the exercises in Chapter 4 and Chapter 5, but want to work through the exercises in this chapter:

1. In a terminal window, create a base directory and subdirectories as described in Section 1.3.
2. Copy the file `1ett_dock_pv.mae` from the directory `$SCHRODINGER/impact-v`*version*`/tutorial/glide/` to the *yourpath*`/tutorial/glide` directory.
3. In the *yourpath*`/tutorial/glide` directory, start Maestro (see Section 1.4).

## 6.2 Displaying Pose Data

The following instructions describe how to open a pose viewer file in the Glide Pose Viewer panel. When the file is opened, the ranked list of scored poses is displayed in the panel and the receptor and the first ligand structure in the file are included in the Workspace.

1. In the main Maestro window, choose Glide Pose Viewer from the Tools menu.

   The Glide Pose Viewer panel is displayed.

2. In the Poses tab, click Open.

   The Read Pose Files file selector is displayed.

3. In the *yourpath*`/tutorial/glide` directory, select the `1ett_dock_pv.mae` file (or, if you used distributed processing in Chapter 5, the `1ett_dock_1_50_pv.mae` file) and click Open.

The ligand poses in the file are listed in the Pose Viewer panel, as shown in Figure 6.1. Each ligand pose is identified by index number, title, ligand number, conformation number, and pose number. For each pose, the table gives the GlideScore (G-Score), E-Model, Energy, and various contact counts associated with the pose-receptor combination. Some of these pose properties are examined later in this chapter.

As discussed in Section 5.7, your docking job may have produced slightly different scores from the example used in this guide, and therefore the ranking of lower-scoring ligands may differ slightly from that shown in Figure 6.1.

Now display only the ligand:

1. In the Pose Viewer panel, deselect the Display option.

   The receptor structure is cleared from the Workspace. This is helpful if you want to examine the structure of a selected ligand or if you want to center the display on a ligand before redisplaying the receptor.

2. On the toolbar, click the Fit to screen button.

   The ligand is resized and repositioned in the Workspace so that the structure is entirely visible.

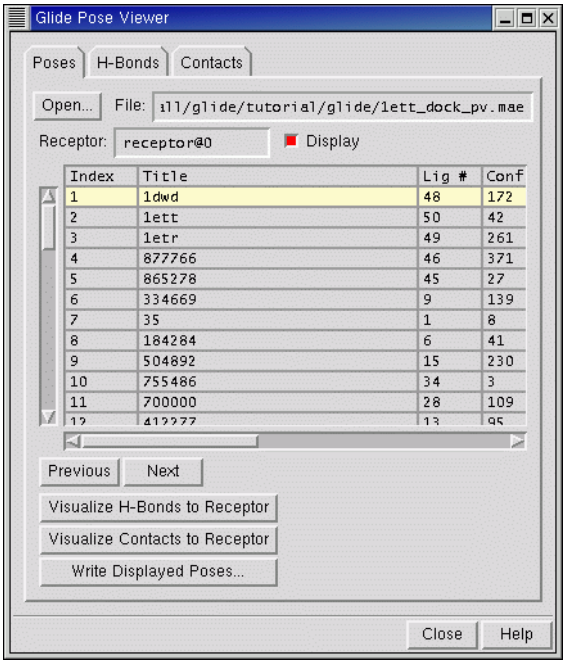


***Figure 6.1. The** Poses **tab of the** Glide Pose Viewer **panel.***

## 6.3 Viewing Poses

When you opened the Glide Pose Viewer panel, pose 1 was automatically selected and displayed. Use the steps below to select ligand poses from the table and display the corresponding structures in the Workspace.

1. Add pose 2 to the selection by shift-clicking the second entry in the pose list.
2. Click Next to select and display only pose 3.
3. Reselect pose 1 by clicking twice on the Previous button.

Instead of using the Glide Pose Viewer to examine the docked ligand structures, you can import the pose viewer file into the Project Table and use the ePlayer. However, the ePlayer cannot show contacts and hydrogen bonds. For information on using the ePlayer, see Section 2.4.1 on page 15, the online help, or Section 8.6 of the *Maestro User Manual*.

## 6.4 Displaying Atoms by Proximity

In this section, you will select a display that includes the ligand and the receptor residues nearest the ligand. This is useful for examining contacts and hydrogen bonds between the ligand and the active site of the receptor.

1. In the Poses tab of the Glide Pose Viewer panel, select Display.

   The receptor is redisplayed in the Workspace.

2. Choose Molecule Number (Carbons) from the Color by scheme button menu.

   

3. On the toolbar, click Display only and choose Select from the menu.

   

   The Atom Selection dialog box opens with the heading Select to Display Only.

4. Click the Molecule tab and select Molecule Number.

5. In the Workspace, click on an atom in the ligand.

   The ligand molecule is marked in purple.

6. In the Atom Selection dialog box, click Add (in the upper right portion of the panel).

   The markers on the ligand molecule turn cyan.

7. Click Proximity (in the lower right portion of the panel).

   The Proximity dialog box is displayed.

8. Ensure that Within and Angstroms are selected, and type 5 in the text box.

9. Under Fill, select Residues.

10. Click Update Markers.

    The cyan trace markers now include several nearby residues as well as the ligand.

11. Click OK to close the Proximity dialog box, then click OK to close the Atom Selection dialog box.

    Only the ligand and the nearby residues are displayed. All residues that do not have any atoms within 5 Å of the ligand are undisplayed. Hiding the residues that do not come into contact with the ligand makes it easier to examine the ligand-receptor interactions.

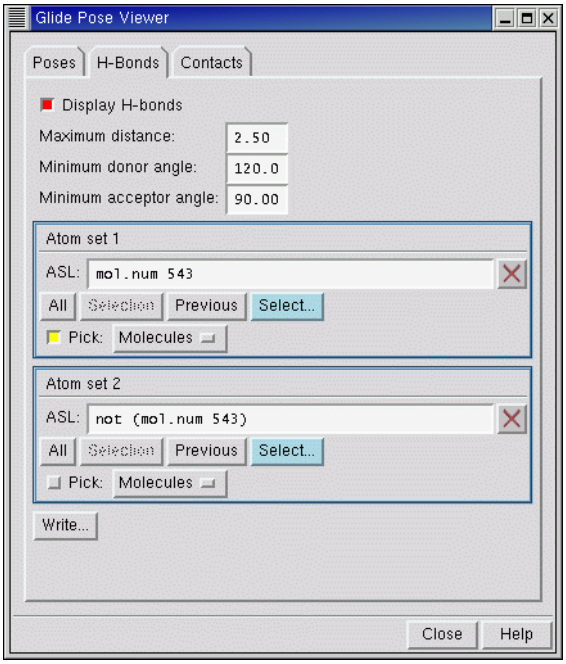


***Figure 6.2. The** H-Bonds **tab of the** Glide Pose Viewer **panel.***

## 6.5 Visualizing Hydrogen Bonds

Use the following instructions to display hydrogen bonds between the ligand and the receptor. (To display hydrogen bonds between any two sets of atoms, use the Atom set 1 and Atom set 2 selection options in the H-Bonds tab.)

1. In the Poses tab, ensure that Display is selected and that the ligand selected is ligand 1 (`1dwd`).

   The HBnd column of the poses list for the selected ligand reports four hydrogen bonds.

2. In the H-Bonds tab, ensure that Display H-Bonds is selected.

3. In the Poses tab, click Visualize H-Bonds to Receptor.

   The four hydrogen bonds between the ligand and the receptor are depicted in the Workspace as broken yellow lines.

## 6.6 Visualizing Bad and Ugly Contacts

In the pose list, 345 Good vdW, 10 Bad vdW, and 3 Ugly vdW contacts are reported for 1dwd. Even the least-good ligand pose has many more good contacts than bad or ugly ones. The default is to display only Bad or Ugly contacts between the ligand and the receptor. (To display contacts between any two sets of atoms, use the Atom set 1 and Atom set 2 selection options in the Contacts tab.)

1. In the Poses tab of the Glide Pose Viewer panel, ensure that Display is selected.
2. In the Contacts tab, make sure Display contacts is selected.

   Note that you can modify the Contact cutoff ratios to redefine the distance criteria for Good, Bad, and Ugly contacts.
3. In the Poses tab, ensure that ligand 1 (1dwd) is selected.
4. Click Visualize Contacts to Receptor.

   The contacts are shown as dashed lines connecting Workspace atoms. There are three Ugly contacts, shown in red, but these are hydrogen bonds (the red markers are obscured by the yellow hydrogen bond markers.) There are several Bad contacts, shown in orange.

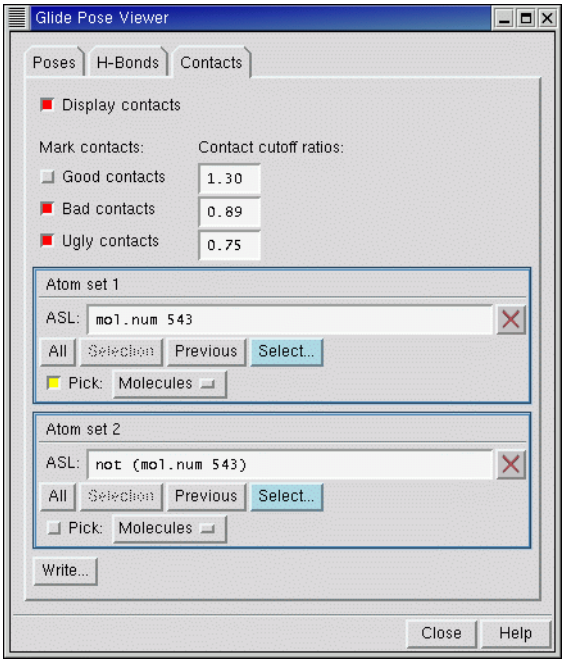


***Figure 6.3. The** Contacts **tab of the** Glide Pose Viewer **panel.***

## 6.7 Writing a File Containing a Single Ligand

In the previous exercise, you used the Glide Pose Viewer's measurement and display tools to view ligand-receptor interactions. The instructions below describe how to create structure files for the top poses in the pose viewer file. Liaison is one application that requires individual structure files.

1. In the Poses tab of the Glide Pose Viewer panel, deselect the receptor Display option.

   The receptor is removed from the Workspace.

2. Select the first pose in the pose list.

3. Click Write Displayed Poses.

   The PoseWrite panel is displayed.

4. Ensure that Append is deselected, and then click Write To.

   The Write Pose File file selector is displayed.

5. Navigate to the *yourpath*`/tutorial/lia_structures` directory.

6. After the text in the Selection text box, type `1ett_poses.mae`.

7. Click Save.

   The first ligand pose is written to the structure file `1ett_poses.mae`.

8. Repeat the previous steps to write each of the first five poses to its own structure file, starting again with pose 1. This time, name the files using the pose number and the title of the ligand pose, in the format `pose`*#_ligandtitle*`.mae`—for example, `pose1_1dwd.mae`.

When you are finished with the steps above, you will have written six files: five suitable for use as input for Liaison jobs, and one to use in the next exercise.

## 6.8 Saving Multiple Ligand Poses to a Single File

There are two ways to save multiple ligand poses to a single file: select multiple ligands from the list simultaneously or append structures to an existing file.

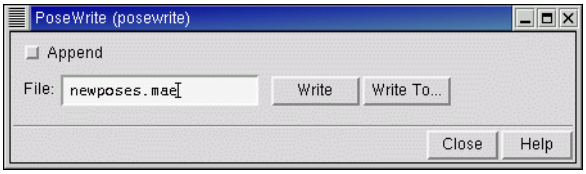


***Figure 6.4. The** PoseWrite **panel.***

To save multiple structures to the same file simultaneously, shift-click to select a range of poses, then use the steps for writing displayed poses outlined in Section 6.7.

In this exercise, you will append a single structure to the `1ett_poses.mae` file, using the procedure for saving additional structures one at a time to an existing file.

1. In the Poses tab, select the second entry in the Pose List.
2. Click Write Displayed Poses.
3. In the PoseWrite panel, select Append.
4. Click Write To.
5. Select `1ett_poses.mae` in the Files list and click Save.
6. Close the PoseWrite and Glide Pose Viewer panels.

Whether you write structures to the file one by one or in groups, when you import the file into a Maestro project, each structure becomes a separate entry.

## 6.9 Finishing the Exercise

Close the scratch project you are working in. Because you have written the output structure files to your directory tree, you do not need to save the scratch project or Workspace structures. Click OK to delete any scratch entries.

Choose Quit from the Maestro menu and click Quit, do not save log file. (For more information about Quit panel options and `maestrolog.cmd` files, click Help instead.)

# Getting Help

Schrödinger software is distributed with documentation in PDF format. If the documentation is not installed in `$SCHRODINGER/docs` on a computer that you have access to, you should install it or ask your system administrator to install it.

For help installing and setting up licenses for Schrödinger software and installing documentation, see the *Installation Guide*. For information on running jobs, see the *Job Control Guide*.

Maestro has automatic, context-sensitive help (Auto-Help and Balloon Help, or tooltips), and an online help system. To get help, follow the steps below.

- Check the Auto-Help text box, which is located at the foot of the main window. If help is available for the task you are performing, it is automatically displayed there. Auto-Help contains a single line of information. For more detailed information, use the online help.
- If you want information about a GUI element, such as a button or option, there may be Balloon Help for the item. Pause the cursor over the element. If the Balloon Help does not appear, check that Show Balloon Help is selected in the Help menu of the main window. If there is Balloon Help for the element, it appears within a few seconds.
- For information about a panel or the tab that is displayed in a panel, click the Help button in the panel. The Help panel is opened and a relevant help topic is displayed.
- For other information in the online help, open the Help panel and locate the topic by searching or by category. You can open the Help panel by choosing Help from the Help menu on the main menu bar or by pressing CTRL+H.

  To view a list of all available Glide–related help topics, choose Glide from the Categories menu of the Categories tab. Double-click a topic title to view the topic.

If you do not find the information you need in the Maestro help system, check the following sources:

- *Maestro User Manual*, for detailed information on using Maestro
- *Maestro Tutorial*, for a tutorial on the basic features of Maestro
- *Maestro Command Reference Manual* for information on Maestro commands
- *Glide User Manual*, for detailed information on using Glide
- *Impact Command Reference Manual*, for information on Impact commands
- Frequently Asked Questions pages, at https://www.schrodinger.com/Glide_FAQ.html

The manuals are also available in PDF format from the Schrödinger Support Center. Information on additions and corrections to the manuals is available from this web page.

If you have questions that are not answered from any of the above sources, contact Schrödinger using the information below.


E-mail: help@schrodinger.com
USPS: 101 SW Main Street, Suite 1300, Portland, OR 97204
Phone: (503) 299-1150
Fax: (503) 299-4532
WWW: http://www.schrodinger.com
FTP: ftp://ftp.schrodinger.com


Generally, e-mail correspondence is best because you can send machine output, if necessary. When sending e-mail messages, please include the following information, most of which can be obtained by entering `$SCHRODINGER/machid` at a command prompt:

- All relevant user input and machine output
- Glide purchaser (company, research institution, or individual)
- Primary Glide user
- Computer platform type
- Operating system with version number
- Glide version number
- Maestro version number
- mmshare version number

# Copyright Notices

### C and C++ Libraries for Parsing PDB Records

# Glossary

**Base Name**—The name entered in the Base name for grid files text box that is used to write grid files during a grid file calculation, or to find pre-existing grid files during a docking job.

**Bounding Box**—The green, cube-shaped marker that appears in the Workspace during Glide docking job setup after you select active site residues, coordinates, or a ligand to be used as the box's center. The box represents the space in which ligands are allowed to move during docking. Increasing the size of the bounding box increases the space that can be sampled by the docked ligands, and consequently increases the CPU time required for the calculation.

**Contacts**—Graphical representations of the van der Waals interactions between the atoms of two or more molecules. Within Maestro, contacts are categorized as "Good," "Bad," and "Ugly." Good contacts are those that have van der Waals radii consistent with the experimentally determined values for the involved atom types. Bad contacts depict those interactions that are experimentally improbable. Ugly contacts represent van der Waals interactions that are disallowed in experimental systems.

**Enclosing Box**—The purple, cube-shaped marker that appears in the Workspace after you specify active residue sites, coordinates, or a ligand to be used as a bounding box center using the Glide panel. The enclosing box represents the space that any part of any specified ligand can sample during a docking calculation. Compare this with the green *bounding box*, which represents the space that the center of each specified ligand must be confined to during a docking calculation.

**Flexible Docking**—A job type in which alternate conformations for each ligand are generated during the docking process, and then the interactions between the receptor and the conformers are analyzed. After docking jobs are complete, the conformers, or "poses," are ranked according to their overall interaction with the receptor. The results can be posted to a pose view file, which can be examined using the Glide Pose Viewer panel.

**GlideScore**—Glide's scoring function (based on ChemScore). GlideScore is used in ranking ligand poses found in docking. In Liaison, GlideScore is used in an alternative binding energy model.

**Grid Files**—Files written by Glide during grid setup. These files contain data about the properties of the associated receptor and are used during docking.

**Ligand Centroid**—Used to define the enclosing box center, a ligand centroid is the point whose x, y, and z coordinates are the mean of the minimum and maximum *x*, *y*, and *z* coordinates of all the atoms in the ligand.

**Pose Viewer Panel**—An analysis tool that displays the results of Glide docking jobs. These results, which are recorded in a pose view file, include the ligand name, pose number, overall score, number of contacts, and other data. The poses within the file are arranged in the list according to score: ligands with the most energetically favorable interactions with the receptor appear at the beginning, and ligands with less favorable interactions appear near the end. The Glide Pose Viewer panel can also be used to visualize contacts and hydrogen bonds between ligand and receptor molecules, or to write structure files containing one or more ligand poses.

**Reference Ligand**—A user-specified structure whose ligand/receptor docking score will be compared with all other docked ligands.

**Rigid Docking**—A job type in which only supplied conformations of the specified ligands will be docked, scored, and displayed in a pose view file. This job type is useful if you have already performed a conformational search on the ligands that you want to dock.

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## W

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